A COMPARATIVE EVALUATION OF THE EFFICACY AND SIDE-EFFECT PROFILE OF SIMVASTATIN Vs ATORVASTATIN IN DYSLIPIDEMIC PATIENTS

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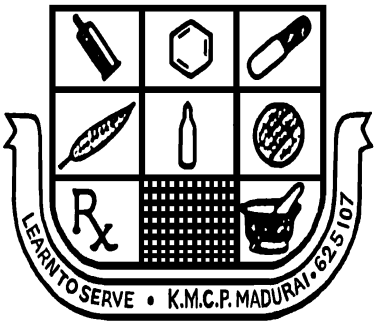

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CERTIFICATE

This is to certify that the dissertation entitled **"A COMPARATIVE EVALUATION OF THE EFFICACY AND SIDE-EFFECT PROFILE OF SIMVASTATIN Vs ATORVASTATIN IN DYSLIPIDEMIC PATIENTS"** submitted by **Ms. Emelia Theresa Thomas**, to The Tamilnadu Dr. M.G.R Medical university, Chennai**,** in partial fulfillment of the requirement for the award of **Master of Pharmacy in Pharmacy Practice**, at **K.M.College of Pharmacy,** Uthangudi, Madurai-107, is a bonafide work carried out by her under my guidance and supervision during the academic year of 2011 – 2012. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

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1. INTRODUCTION

Cardiovascular Diseases (CVD) are the most prevalent cause of death and disability in both developed as well as developing countries.[1] South Asians around the globe have the highest rates of Coronary Artery Disease (CAD).[2] According to National Commission on Macroeconomics and Health (NCMH), a Government of India undertaking, there would be around 62 million patients with CAD by 2015 in India.[3] Thus the prevalence of CVD is expected to increase in the next decade, predominantly because of increasingly sedentary lifestyles and an attendant increase in the prevalence of obesity and diabetes mellitus.

CAD is usually due to atherosclerosis of large and medium sized arteries. Atherosclerosis is a multifocal, smoldering, immunoinflammatory disease of the artery undergoing gradual lipid deposition and intima thickening, resulting in elasticity decrease, lumen occlusion and reduced blood flow [4, 5]. Such a diffuse process may start early in childhood and progresses asymptomatically through adult life as a relatively benign disease that is rarely fatal by itself.[6] The most devastating complications of atherosclerosis, i.e. life-threatening clinical events, such as acute coronary syndrome and stroke, are provoked by arterial occlusion precipitated by atherosclerotic plaque erosion or disruption with superimposed thrombosis. This process is defined as atherothrombosis.[6, 7] The most common complications of this pathologic condition are ischemic heart disease, heart attacks, cerebral strokes (CVA), and brain degeneration.

Development of atherosclerosis involves multiple metabolic and cellular processes.[8, 9] It is generally considered a chronic inflammatory disease developing as a response to endothelial activation and dysfunction that leads to progressive vasoconstrictive impact and proinflammatory, prothrombotic, procoagulative and proliferative processes in the vessel wall, i.e. initiates the sequence of successive reactions prompting composition of atherosclerotic plaque.[10]

Patients with central obesity, insulin resistance, hypertension, and type 2 diabetes mellitus have a unique dyslipoproteinaemia characterized by hypertriglyceridemia,

elevated levels of small dense low-density lipoprotein (LDL) cholesterol, and low levels of HDL cholesterol. Thus lipoproteins are the major risk factors in cardiovascular disease.

Correlations between coronary artery disease and the properties, compositions, and plasma concentrations of various lipid and lipoproteins have revealed mechanisms that ultimately aid diagnosis and provided new targets for pharmacological management of dyslipidemia and atherosclerosis.

Blood lipid assessment forms an essential step in the assessment of almost every cardiac patient, whether middle aged or elderly. Risk factor assessment is integral to the cardiovascular management of all patients. Regrettably, large numbers of drug-eligible patients who may benefit from statins and other lipid lowering drugs are still not receiving them.[11]

The main focus in treating lipid disorders is on reducing LDL-cholesterol concentrations. Also, lipid-related independent risk factors, such as triglyceride, HDL cholesterol, and lipoprotein (a) levels should be used clinically to assess the cardiovascular risk.

1.1. DYSLIPIDEMIA

Dyslipidemia is the term given to abnormalities in blood levels. Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction and deficiency.[12] They may manifest as one or more of the following:

- Elevated Total Cholesterol
- Elevated low Density Lipoprotein
- Elevated Triglycerides
- Decreased High Density Lipoprotein Cholesterol (HDL).

Disorders of lipoprotein metabolism, together with the prevalence of high-fat diets, obesity, and physical inactivity, have resulted in an epidemic of atherosclerotic disease in the developing countries. The interaction of common genetic and acquired disorders of

lipoproteins with these adverse environmental factors predisposes to premature atherosclerosis.

The recognition that low levels of High Density Lipoprotein (HDL) and the presence of small dense low Density Lipoprotein (LDL) particles are clinically important in the development of CAD has led to the use of term dyslipidemia to describe a range of disorders that include both abnormally high and low lipoprotein levels as well as abnormalities in the composition of these particles. Thus Dyslipidemia is clinically important to atherogenesis.

1.2. CLASSIFICATIONS OF DYSLIPIDEMIAS

Dyslipidemia can be classified in two ways:

- **First classification** depends on measurement of the concentrations of plasma triglycerides, Total cholesterol and HDL cholesterol.[13]

Table No: 1

Cholesterol Disorders	Cholesterol level elevated and exceeds triglyceride concentration
Triglyceride Disorders	Triglyceride level elevated and exceeds Cholesterol concentration
HDL cholesterol concentration reduced	<35 mg/dl

Hypercholesterolemia is associated with an increased concentration of one or more of the cholesterol-carrying lipoproteins (LDL, VLDL, HDL), which may occur because of a higher concentration of cholesterol in each particle, an increased number of particles, or a combination of both. Both VLDL and LDL particles contain one apolipoprotein B-100 molecule and, therefore, an elevation of the apolipoprotein B concentration reflects an increased number of cholesterol-containing particles, which is associated with

hypercholesterolemia. The most common cause of hypercholesterolemia is an elevation in LDL cholesterol.[14]

The most studied forms of dyslipidemia are familial hypercholesterolemia. These patients have a defective gene from one or both parents for the B-E/LDL receptor, significantly reducing their ability to clear LDL from the blood. Homozygous familial hypercholesterolemia can result in four to six times the normal concentrations of cholesterol and significant atherosclerotic disease, detected during the teenage years. Heterozygous familial hypercholesterolemia can cause two to four times the normal concentrations of cholesterol with premature atherosclerotic disease.[14, 15]

Hypertriglyceridemia occurs in patients with high concentrations of VLDL or chylomicron particles. Most cases are mild and are primarily caused by increased VLDL secretion by the liver in patients who consume an excessive amount of calories or alcohol (diet-induced hypertriglyceridemia). VLDL secretion can also increase secondary to diabetes, obesity, or other medical problems (secondary hypertriglyceridemia). Primary hypertriglyceridemia occurs because of an overproduction of triglycerides and VLDL particles and is often associated with other medical conditions including diabetes and obesity. Hypertriglyceridemia is not usually an isolated condition. It tends to be associated with patients who have low concentrations of HDL cholesterol and elevated levels of LDL particles, posing the risk for atherogenesis. Mixed hyperlipidemias are the most common forms of dyslipidemia where patients may have elevations in both triglyceride and cholesterol levels.

Patients with reduced HDL cholesterol concentrations often have normal total cholesterol concentrations and normal or only slightly elevated LDL cholesterol levels. As a consequence, their LDL levels may not be elevated enough to meet the National Cholesterol Program guidelines for drug therapy despite the well-accepted fact that these patients are at increased risk of developing coronary heart disease.[16]

- **Second classification** is Fredrickson classification which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. There are two major ways in which dyslipidemia are classified.[17]

a) Phenotype

Table No: 2

Lipoprotein Patterns (Fredrickson Phenotypes)		
Phenotype	**Elevated Lipoprotein(s)**	**Elevated Lipids**
I	**Chylomicrons**	**TGs**
IIa	**LDL**	**Cholesterol**
IIb	**LDL and VLDL**	**TGs and cholesterol**
III	**VLDL and chylomicron remnants**	**TGs and cholesterol**
IV	**VLDL**	**TGs**
V	**Chylomicrons and VLDL**	**TGs and cholesterol**

b) Etiology

Primary causes:

Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL.

Secondary causes:

The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats. Other common secondary causes include diabetes mellitus, alcohol overuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis and other cholestatic liver diseases, and drugs, such as thiazides, β-blockers, retinoids, highly active antiretroviral agents, estrogen and progestins, and glucocorticoids.

1.3. EPIDEMIOLOGY

Heart disease and stroke are the principal components of cardiovascular disease. Heart disease and stroke are usually due to atherosclerosis of large and medium sized arteries. Hypercholesterolemia is the most important factor in the pathogenesis of atherosclerosis.[18, 19]

Hypertension, smoking, diabetes, obesity, physical inactivity, and atherogenic diets have all been identified as modifiable risk factors for heart disease. Age, male gender, and a family history of premature coronary heart disease (CHD) have been identified as non modifiable risk factors.[20]

The National Cholesterol Education Program Adult Treatment Panel on Detection, Evaluation, and Treatment Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP) published NCEP ATP I, NCEP ATP II, [13] and most recently NCEP ATP III.[21] The executive summary of NCEP ATP III was published in May 2001.[22] The full report of NCEP ATP III was published in December 2002. The NCEP is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH).[21]

HISTORICAL PERSPECTIVE

Based on Framingham Heart Study results reported in 1961, the concept of risk factors for coronary heart disease was clearly established. Hypertension and hypercholesterolemia were initially identified as major contributors to cardiovascular disease.[23] The NCEP guidelines were updated in 1993, and the "Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," also known as Adult Treatment Panel (ATP III), was issued in 200l.

ASSESSING RISK IN ASIAN INDIANS

The common pattern of dyslipidemia seen in Asia Indians when compared to the lipid profile of white Americans is listed in Table.No:3[24, 25, 26, 27] Asian Indians tend to have higher levels of triglycerides, lower HDL levels, and higher levels of Lp (a).

Table No: 3

Pattern of Dyslipidemia among Asian Indians Relative to American Whites.	
Lipid	**Relative Serum Concentration**
TC	Similar
LDL	Similar
Triglycerides	Higher
HDL	Lower
Lp(a)	Higher

Total cholesterol levels and LDL levels are correlated with extent and severity of CHD in Asian Indians as in whites. But at any given total cholesterol or LDL level, Asian Indians have a greater CHD risk than whites.[28, 29] Therefore, Asian Indians with dyslipidemia should be treated as aggressively as if they had a CHD risk equivalent similar to the treatment of patients with diabetes or heart disease. Thus, while a total cholesterol level of <200 mg/dL is desirable according to the Framingham model for those with 0 to 1 risk factor, the goal for the Asian Indian population should be <160 mg/dL. An LDL level of <160 mg/dL is appropriate for most Americans with 0 to 1 risk factor, but a level of <100 mg/dL is optimal for Asian Indians.[30]

HDL levels of 60 mg/dL are considered optimal in both whites and Asian Indians. HDL levels are considered low when they drop below 40 mg/dL. However, most experts consider a level <50mg/dL to be low in women.[31]

The acceptable "normal" level of triglycerides was decreased from <200 mg/dL in the ATP II report to <150 mg/dL in the ATP III classification. Lipoprotein (a) is still considered an emerging risk factor in the US population at large, but appears to be a major risk factor in Asian Indians.[32, 33, 34, 35, 36] A high level of Lp (a) is the most prevalent dyslipidemia in patients with premature CHD. Lp (a) levels are governed almost exclusively by race, ethnicity, and genetics, unlike other lipids, where the levels are influenced by age, gender, diet, and other environmental factors. Although Lp(a) levels >30 mg/dL are generally considered the threshold at which high risk of premature CHD increases rapidly, levels below 20 mg/dL are considered optimum, particularly in Asian Indians.[37]

When combined with concomitant elevation of triglycerides, and LDL, and decreases in HDL concentrations, the pathophysiological effects of elevated Lp (a) are exponentially increased.[38] This "deadly lipid quartet," commonly present in Asian Indians, usually results from affluent lifestyles led by immigrants, as well as those living in urban areas in India.[39] The high rates of CHD in Asian Indians are due to a combination of genetic predisposition and lifestyle factors.

PREVENTION OF CHD IN ASIAN INDIANS

The most important aspect of preventing CHD is identifying individuals at high risk of developing CHD at an early age. Since Lp (a) is fully expressed in the first year of life, tracking Lp (a) from childhood may be a better option than focusing on other dyslipidemia that are not expressed until later life.[39] This is particularly true of those with a family history of premature CHD.

Modification of lifestyle, such as increasing physical activity and decreasing consumption of calories particularly saturated fat should begin early in life. Abdominal obesity should be avoided. Consumption of all types of tobacco products should be eliminated. Appropriate drug therapy should be considered for all lipid abnormalities and risk factor abnormalities, which do not respond to lifestyle adjustment.[40, 41, 42]

1.4. LIPIDS AND LIPOPROTEINS

The French Physician-scientist **Michel Macheboeuf** is known as the **Father of plasma lipoproteins.**[43] Lipids are a chemically diverse group of compounds that are poorly soluble in the aqueous environment of the cell. The main ones being cholesterol, triglyceride and phospholipids. Lipids are transported in plasma as components of lipoprotein complexes. Lipoproteins are spherical complex particles composed of neutral lipids, polar lipids and specialized proteins called apolipoproteins (apos).

The lipids are mainly free and esterified cholesterol, triglycerides, and phospholipids. The hydrophobic triglyceride and cholesteryl esters (CEs) compose the core of the lipoproteins, which is covered by a unilamellar surface that contains mainly the

amphipathic (both hydrophobic and hydrophilic) phospholipids and smaller amounts of free cholesterol and proteins.

Apolipoproteins are the proteins on the surface of the lipoproteins. They not only participate in solubilizing core lipids but also help in the regulation of plasma lipid and lipoprotein transport.[44]

Lipids have important roles in virtually all aspects of life: serving as hormones, serving as an energy source, aiding in digestion, acting as structural components in cell membrane. In addition, lipid and lipoproteins are intimately involved in the development of atherosclerosis, a pathogenic process that is the underlying cause of the common cardiovascular disorders of MI, cerebrovascular diseases, PVD.[45]

CLASSIFICATION OF LIPOPROTEINS

Based on their densities, lipoproteins have been classified into: [46]

- Chylomicrons
- Very Low Density Lipoproteins (VLDL)
- Intermediate Density Lipoproteins (IDL)
- Low Density Lipoproteins (LDL)
- High Density Lipoproteins (HDL)

Table No: 4

Lipoprotein	Density (g/dL)	Diameter (nm)	Lipid (%)		
			TG	Chol	PL
Chylomicrons	0.95	75-1200	80-95	2-7	3-9
VLDL	0.95-1.006	30-80	55-80	5-15	10-20
IDL	1.006-1.019	25-35	20-50	20-40	15-25
LDL	1.019-1.063	18-25	40-50	40-50	20-25
HDL	1.063-1.210	5-12	15-25	15-25	20-30

CHYLOMICRONS

Chylomicrons are synthesized in the absorptive cells in the small intestine and transport dietary triglyceride from the small intestine via the lymph into plasma. They are the largest lipoprotein and are rich in triglycerides.[47] They consist of highest quantity of lipids (99%) and lowest concentration of proteins (1%). They contain 90% to 95% of triglycerides, 2% to 6% phospholipids, 2% to 4% cholesteryl ester, 1% free cholesterol and 1% to 2% apolipoprotein. Apolipoproteins present are apo C and apo B-48 (most abundant) along with small amounts of apo E, AI, AII and AIV. They are not found in 12 to 24 hour fasting specimens. Chylomicrons transport exogenous lipids to liver, adipose, cardiac, and skeletal muscle tissue. The capillary beds of these tissues contain high concentrations of LPL. LPL hydrolyzes TG in the chylomicrons into free fatty acids that are either oxidized by the muscle cells to generate energy. Once the chylomicrons have been processed by LPL, the TG depleted chylomicron is called as chylomicron remnants which is the transported into the liver.[48]

VERY LOW DENSITY LIPOPROTEIN

VLDL is a triglyceride rich lipoprotein and constitutes about 10% to 15% of total serum cholesterol. VLDL is produced in liver and intestine and is responsible for the transport of endogenous triglycerides. It is made up of 50% to 65% triglyceride, 8% to 14% cholesteryl ester, 12% to 16% phospholipids, 4% to 7% free cholesterol and 5% to 10% apolipoprotein. Excess carbohydrate diet increases triglyceride synthesis of liver resulting in increased production of VLDL. VLDL transports endogenous triglycerides, phospholipids, cholesterol, and cholesteryl esters. It functions as the body's internal transport mechanism for lipids.[49]

INTERMEDIATE DENSITY LIPOPROTEIN

Intermediate-density lipoproteins are the remnant lipoproteins which are the lipolytic products of catabolism of the VLDL. They are cleared from the plasma into the liver by receptor-mediated endocytosis, or further degraded to form LDL particles. It transports a variety of triglyceride fats and cholesterol and, like LDL, can also promote the growth of atheroma.[50]

LOW DENSITY LIPOPROTEIN

LDL is formed from VLDL in the blood circulation and liver. They are involved in the transport of cholesterol from liver to other tissues. They contain 50% cholesterol. It is made up of 35% to 45% cholesteryl esters, 6% to 15% free cholesterol, 22% to 26% phospholipids, 4% triglycerides and 22% to 26% apolipoprotein. LDL is the major atherogenic lipoprotein, and is the primary target for cholesterol lowering therapy. LDL is the primary plasma lipid carrier with a single apolipoprotein (apo) molecule B-100 per one particle.

LDL is oxidized in micro domains in the arterial wall where it is sequestered by proteoglycans and other extra cellular matrix constituents and protected from plasma antioxidants. Oxidized LDL has been shown to be chemotactic and may recruit monocytes into the arterial wall where they can be transformed into foam cells. Oxidized LDL can also be cytotoxic which damage the endothelial cells and promote cellular secretion of several potentially atherogenic molecules.

HIGH DENSITY LIPOPROTEIN

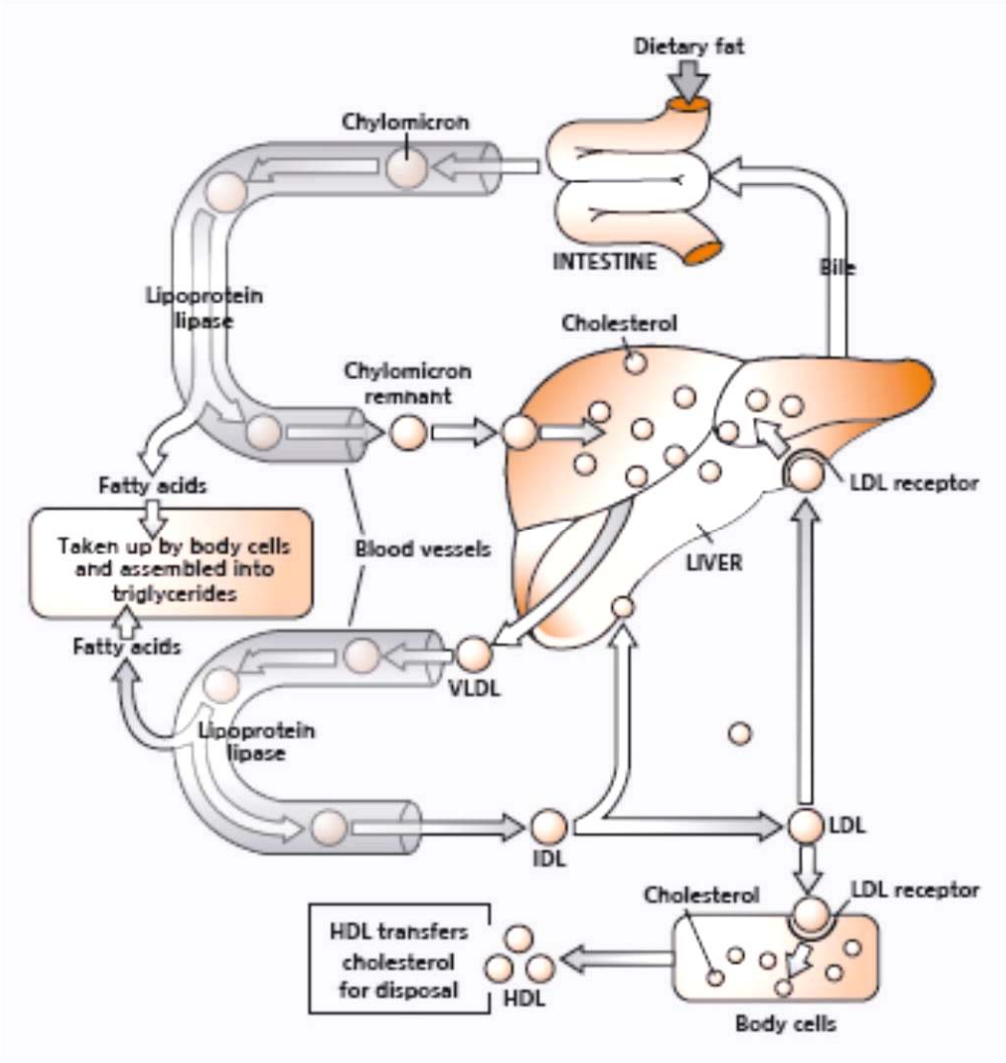
High density Lipoproteins are secreted from the liver as disk-shaped nascent particles that consist primarily of phospholipids, apo A-I and apo AII. HDL constitutes about 20% to 30% of total serum cholesterol. It is thought to protect against the development of atherosclerosis. They are involved in reverse cholesterol transport. They contain 25% to 30% phospholipids, 15% to 20% cholesteryl esters, 5% free cholesterol, 3% triglyceride and 45% to 59% apolipoprotein. There are three subtypes of HDL, in which HDL is considered to be the most antiatherogenic HDL subtype.[51]

1.5. LIPIDPROTEIN METABOLISM

The Pathways of lipoprotein metabolism are complex.[52, 53, 54] They include **Exogenous pathway and Endogenous pathways** based on whether they carry lipids of dietary or hepatic origin and other pathways such as the **Intracellular LDL receptor pathway and the HDL Reverse cholesterol pathway.**

Fig No: 1

Lipid Synthesis, Metabolism and Transport



Exogenous (Dietary) Lipid Pathway:

Following digestion and absorption of dietary fat, TG and cholesterol are packaged to form chylomicrons in the epithelial cells of the intestine. Nascent Chylomicrons are assembled from dietary triglycerides and cholesterol in the enterocytes and packaged in secretory vesicles in the Golgi apparatus. These particles are then transported by exocytosis and introduced into circulation through the intestinal villi. On entering the circulation, these acquire the C apolipoproteins and apo E from circulating HDL. The Apo C activates the LPL attached to the luminal surface of endothelial cells, which rapidly hydrolyzes the triglycerides into free fatty acids. The fatty acids are either taken up by muscle cells as an energy source or into adipose cells for storage.[55]

Endogenous Pathway:

The endogenous pathway involves the liver synthesizing lipoproteins. TG and cholesterol esters are generated by the liver and packaged into VLDL particles and then released into the circulation. VLDL is then processed by LPL in tissues to release fatty acids and glycerol. Once processed by LPL, the VLDL becomes a VLDL remnant. The majority of the VLDL remnants are taken up by the liver via the LDL receptor, and the remaining remnant particles become IDL, a smaller, denser lipoprotein than VLDL. The fate of some of the IDL particles requires them to be reabsorbed by the liver (again by the LDL receptor). However, other IDL particles are hydrolyzed by hepatic-triglyceride lipase to form LDL, a smaller, denser particle than IDL. LDL is the main carrier of circulating cholesterol within the body.

Low Density Lipoprotein Receptor Pathway:

Specific receptors present in coated pits on plasma membranes recognize and bind apo B-100 of LDL. The LDL particles are internalized in coated vesicles, which then fuse to form an endosome. LDL dissociates from the receptor, which returns to the cell surface for reuse, whereas LDL migrates to the lysosome. Once the LDL is delivered to the lysosome, apo B-100 is degraded to small peptides and amino acids.

LDL is also taken up by extra hepatic tissue through scavenger receptors or non-receptor mediated pinocytosis. Macrophages that become enlarged with cholesteryl esters are called "foam cells", and are considered the earliest components of the atherosclerotic lesion.[56]

High-Density Lipoprotein Reverse Cholesterol Transport Pathway:

Reverse cholesterol transport refers to the process by which cholesterol is removed from the tissues and returned to the liver. HDL is the key lipoprotein involved in reverse cholesterol transport and the transfer of cholesteryl esters between lipoproteins.

Through the extracellular addition of surface components of triglyceride-rich particles, such as phospholipids, cholesterol and certain apolipoproteins, nascent HDL is

converted to spherical particles. Free cholesterol from cell membranes is also transferred to the nascent HDL. Cholesterol is esterified by the action of LCAT in the presence of its cofactor apo A-I. The size of the HDL depends on the amount of accumulated cholesteryl esters and the activity of LCAT. Lysolecithin, a byproduct of this reaction is then removed from circulation after binding with albumin. HDL cholesteryl esters are delivered to the liver by one of the following mechanisms: (1) cholesteryl esters are selectively taken up from HDL by the HDL receptors and the HDL particles are returned to circulation for further transport. (2) cholesteryl esters are transferred from HDL to apo B-100 and then taken up by the liver. (3) HDL apo E can be recognized by the hepatic remnant receptors. These processes constitute the reverse cholesterol transport mechanism, by which cellular and lipoprotein cholesterol is delivered back to the liver for reuse or disposal.[53]

1.6. LIPOPROTEIN DISORDERS

There are five primary inherited lipoprotein disorders which disturb lipid metabolism.

These are:

1. **Familial Hypertriglyceridemia (FHTG)**

   It includes lipoprotein lipase (LPL) deficiency, in which low LPL activity results in decreased removal, and thus increases of serum triglyceride, there is increased hepatic secretion and thus raised plasma concentration of triglyceride-rich VLDL. Patients are at risk of recurrent acute pancreatitis when plasma triglyceride exceeds 10mmol/l, and especially 20mmol/l.

2. **Familial combined hyperlipidemia (FCHL)**

   It is common and most important in which there is increased hepatic secretion of apolipoprotein B containing VLDL, and conversion to LDL, in consequence plasma LDL and VLDL are raised. Patients exhibit macro vascular disease.

3. **Remnant removal disease (RRD)**

   It is also called remnant lipaemia, in which there is a defect of apolipoprotein E. This is the major ligand that allows internalization and subsequent metabolism of remnant particles derived from VLDL and

chylomicrons. The consequence is accumulation of VLDL remnants called intermediarte density lipoprotein (IDL) with cholesterol and triglycerides. Patients experience severe macrovascular disease.

4. **Familial hypoalphalipoproteinemia (**rare)

   In which the serum concentration of HDL is low.

5. **Familial hypercholesterolemia (FH)**

   Characterized by elevation of total and LDL cholesterol in plasma. LDL cholesterol is elevated from childhood. The principal consequence is coronary heart disease, but occasionally also peripheral and cerebrovascular disease. It is due to defective LDL receptors or mutation in ligand region of apo B-100.[57]

1.7. CONSEQUENCES OF LIPID ABNORMALITIES[57]

Dyslipidemia is a major risk factor for atherosclerosis. Atherosclerosis is a disease process that affects the coronary, cerebral and peripheral arterial circulation.

Coronary Heart Disease (CHD)

The etiology of atherosclerosis is multifactorial but the cause-effect relationship between dyslipidemia and atherosclerosis has been shown in many studies and trials.

The reducing the plasma LDL cholesterol levels sharply reduces the risk of subsequent clinical CHD in both patients with pre-existing CHD and in patients free of CHD. There is no doubt about the atherogenicity of LDL. Evidence suggests that oxidative modification of LDL within the artery is necessary for mediating its atherogenicity.

An atherogenic lipoprotein pattern, characterized by a predominance of small dense LDL, moderately elevated plasma triglycerides and low HDL levels, is the most powerful risk factor for CAD.

Stroke

Stroke is a term that describes a clinical event caused either by occlusion or hemorrhage in the arterial supply to the central nervous system resulting in tissue infarction. It is one of the most devastating consequences of vascular disease. Atheroma formation is the root of pathogenesis of thromboembolic stroke.

Peripheral Artery Disease (PAD)

Peripheral artery disease is most commonly a manifestation of systemic atherosclerosis in which the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque. High lipoprotein concentrations are important in the development of PAD.

Evidence that atherosclerosis in the peripheral circulation should be considered in the same manner as atherosclerosis in the coronary circulation. Patients with PAD, even in the absence of a history of myocardial infarction or stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with a history of coronary or cerebrovascular disease.

1.8. CLINICAL PRESENTATION

Dyslipidemia usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease.

- High levels of TGs (> 1000 mg/dL [> 11.3 mmol/L]) can cause acute pancreatitis. High levels of LDL can cause eyelid xanthelasmas, arcus corneae, and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints.
- Patients with the homozygous form of familial hypercholesterolemia may have the above findings plus planar or cutaneous xanthomas.
- Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet.

- Patients with the rare dysbetalipoproteinemia can have palmar and tuberous xanthomas.
- Severe hypertriglyceridemia can give retinal arteries and veins a creamy white appearance (lipemia retinalis). Extremely high lipid levels also give a milky appearance to blood plasma.

Diagnosis

Dyslipidemia is diagnosed by measuring serum profile which consists of total cholesterol, TG, and HDL cholesterol and calculated LDL cholesterol and VLDL.

1.9. ASSESSMENT OF LIPID PROFILE

TC, TGs, and HDL cholesterol are measured directly. TC and HDL cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting for maximum accuracy and consistency.

LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually $^1/_5$ of the total lipid in the particle. Thus, LDL cholesterol = TC − [HDL cholesterol + (TGs ÷ 5)] (Friedewald formula). This calculation is valid only when TGs are< 400 mg/dL and patients are fasting, because eating increases TGs.

LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary.[58]

1.10. MANAGEMENT OF DYSLIPIDEMIA

The NCEP guidelines recommend that patients at higher risk of coronary heart disease receive more intensive interventions for dyslipidemia than patients at lower risk.[59] The

ATP III Classification of LDL, Total and HDL Cholesterol and Triglycerides (mg/dL) is shown in Table No: 5

TABLE NO: 5

Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥ 240	High
LDL Cholesterol	
<100	Optimal
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very high
HDL Cholesterol	
< 40	Low
≥ 60	High
Triglyceride	
< 150	Normal
150-199	Borderline high
200-499	High
≥ 500	Very high

Two approaches to therapy are available: lifestyle changes and drug therapy:

- Lifestyle changes are the first step of treatment of dyslipidemia. These include dietary changes, smoking cessation, weight loss (if overweight), and exercise. These changes may reduce cardiovascular disease risk independent of their influence on lipid levels.

- Drug therapy should be reserved for those with known CVD and those patients at increased CVD risk failing to reach LDL-C targets with lifestyle modifications. Statins have been shown to be cost effective in both these populations.

LIFESTYLE MODIFICATIONS

The NCEP guidelines recommend dietary modification, exercise and weight control as the foundation of treatment of dyslipidemia. Cessation of cigarette smoking and reduction of other modifiable risk factors are essential aspects of prevention of coronary heart disease.[60]

EXERCISE AND WEIGHT REDUCTION

Obesity frequently elevates cholesterol levels in both very-low-density lipoprotein (VLDL) and LDL fractions, raises triglyceride levels, lowers HDL cholesterol levels, raises blood pressure and promotes glucose intolerance. Thus Overweight patients should engage in low-intensity exercise more frequently and for longer durations.[61]

ALCOHOL INTAKE

Alcohol exerts several effects on lipid levels, including raising the serum triglyceride and HDL cholesterol levels. Its effect on LDL cholesterol appears to be minimal. The intake of alcohol stimulates the synthesis of triglycerides by the liver. Thus high intake of alcohol usually cause a moderate rise in triglyceride levels, but in patients with an underlying hypertriglyceridemia, the response can be marked i.e., severe hypertriglyceridemia may develop. Thus it is not recommended for the prevention of coronary heart disease.[62]

DIETARY FIBER

Soluble fiber has been shown to modestly reduce total cholesterol and LDL cholesterol levels. Current dietary guidelines recommend a total daily fiber intake of at least 20 to 30 g for adults, with 25 percent of the fiber being soluble fiber. These levels can be attained with the proposed six or more daily servings of grain products and five or more daily servings of fruits and vegetables**.**

ANTIOXIDANTS

Atherogenicity is promoted by oxidation and glycosylation of LDL cholesterol. Several vitamins, including vitamin C, vitamin E and β-carotene, have antioxidant properties, which may provide protection against atherogenesis. Fruits and dark-green and deep-yellow vegetables are rich sources of antioxidant vitamins. Thus the use of antioxidants prevents the formation of oxidized LDL.

DRUG THERAPY

Because dietary modification rarely reduces LDL cholesterol levels by more than 10 to 20 %, the NCEP guidelines recommend that consideration be given to the use of cholesterol-lowering agents if lipid levels remain elevated after six months of intensive dietary therapy or sooner under certain circumstances.[63]

A patient with a very high LDL cholesterol level may need to start drug therapy sooner, because it is unlikely that a patient with an LDL level of 130 mg/dL (3.35 mmol per L) or greater will be able to achieve the goal of 100 mg/dL (2.60 mmol per L) with diet alone.[64]

The currently available lipid-lowering drugs can be divided into the statins, the bile acid sequestrants, nicotinic acid, the fibrates, and cholesterol absorption inhibitors. These all reduce LDC-C. Of these drugs, statins with their relatively few side effects and predictable benefits for treating LDC-C are now usually the drugs of first choice. They are highly effective in reducing total cholesterol and LDC-C, they usually increase HDL-C, and long term safety and efficacy are now established. The lipid lowering drugs with their side effects and contraindications are shown in Table No:6

Table No: 6 Drugs Affecting Lipoprotein Metabolism

Drug Class	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG – CoA reductase inhibitos (Statins) Simvastatin Atorvastatin Rosuvastatin Lovastatin Pravastatin Fluvastatin	LDL ↓18-55% HLD ↑5-15% TG ↓7-30%	Myopathy, Increased liver enzymes	Active or chronic liver disease
Fibric acids (Fibrates) Fenofibrate, Bezafibrate Clofibrate Gemfibrozil	LDL (may be increased in patients with high TG) ↓5-20% HDL ↑10-20% TG ↓ 20-50%	Dyspepsia, Gallstones, Myopathy	Severe renal disease
Nicotinic acid (Niacin)	LDL ↓ 5-25% HDL ↑15-35% TG ↓20-50%	Flushing, Hyperglycemia, Hyperuricemia	Chronic liver disease
Cholesterol Absorption Inhibitors (CAI) Ezetimibe	LDL ↓17% HDL – Minimal change TG – minimal change	Angioedema, Headache	Hypersensitivity
Bile acid Sequestrants (BAR) Cholestyramine Colestipol	LD ↓15-30% HDL ↑3-5% TG no change or increase	Gastrointestinal distress	Dysbetaliporoteinemia

STATINS

The statins are the most effective and best tolerated agents for treating dyslipidemia. These drugs are used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver.[65] Statins have anti atherosclerotic effects, that correlate positively with the

percent decrease in LDL cholesterol. In addition, they can exert antiatherosclerotic effects independently of their hypolipidemic action. This is because mevalonate metabolism generates a series of vital isoprenoids for different cellular functions, from cholesterol synthesis to the control of cell growth and differentiation. Also, statins significantly reduce the incidence of coronary events, both in primary and secondary prevention, being the most efficient hypolipidemic compounds that have reduced the rate of mortality in coronary patients. Beyond lipid-lowering activity, Statins exhibit actions like:

- Improve endothelial function
- Modulate inflammatory responses
- Maintain plaque stability
- Prevent thrombus formation

History

The identification of inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase led to the class of drugs known as statins. The discovery culminated in the labs of Dr. Akira Endo at Sankyo in Japan in the early 1970s.

The first statin isolated was mevastatin (ML-236B), a molecule produced by the fungus *"Penicillium citrinum"*. Mevastatin was never marketed, because of its adverse effects of tumors, muscle deterioration, and death observed in laboratory dogs.

In 1978, Merck & Company isolated their first statin (initially called mevinolin, monacolin K, and MK803) from *Aspergillus terreus.* In 1987, Merck & Company launched the statin lovastatin (Mevacor).[66]

The statins are divided into two groups: fermentation derived and synthetic. Lovastatin, Simvastatin, Pravastatin are derived from fungi while Fluvastatin, Atorvastatin, and Rosuvastatin are synthetic. All statins share an HMG-CoA like moiety, a dihydroxy hepatanoic acid, which competes with HMG-CoA for binding with HMG-CoA reductase.

Mechanism of Action

Statins inhibit HMG-CoA reductase, the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor. They alter the conformation of the enzyme when

they bind to its active site. This prevents HMG-CoA reductase from attaining a functional structure. The change in conformation at the active site makes these drugs very effective and specific. Binding of statins to HMG CoA reductase is reversible, and their affinity for the enzyme is in the nanomolar range, as compared to the natural substrate, which has micromolar affinity.[67]

The inhibition of HMG-CoA reductase determines the reduction of intracellular cholesterol, inducing the activation of a protease which slices the sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs are translocated at the level of the nucleus, where they increase the gene expression for LDL receptor. The reduction of cholesterol in hepatocytes leads to the increase of hepatic LDL receptors, that determines the reduction of circulating LDL and of its precursors (intermediate density - IDL and very low density- VLDL lipoproteins).[68] All statins reduce LDL cholesterol non-linearly, dose-dependent, and after administration of a single daily dose.[69]

Administration

Patients should be started on therapeutic lifestyle changes, such as diet and exercise, prior to the initiation of statin therapy. Statins are best given once daily in the evening to coincide with the cholesterol biosynthesis at night. It is recommended that lovastatin be administered with food to enhance its absorption, but the other statins may be taken with or without food. The LDL cholesterol-lowering effect may be seen within two weeks of initiating therapy, but may take as long as six weeks to be achieved with atorvastatin or rosuvastatin.[70]

Side Effects of Statin Therapy

Statins are generally well tolerated. The most important adverse effects are liver and muscle toxicity.

Drug-induced liver injury is uncommon, but in rare circumstances it may lead to liver failure. It is typically classified as either hepatocellular or cholestatic. Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) indicate liver cell damage, whereas elevations in total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase (GGT) reflect cholestasis. Injury from statins is hepatocellular and is therefore

indicated by elevations in AST and ALT levels. These elevations are usually asymptomatic and transient and resolve after discontinuation of the drug. Thus liver enzymes should be monitored in all patients who take statins. If the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level doubles, the statin should be stopped.[71]

The most common side effect associated with statins is myalgia. The exact mechanism is unknown. One hypothesis is that statins reduce the cholesterol content of the sarcolemma of skeletal muscle cells which may lead to instability or even rupture of some muscle cells.[72] Another hypothesis states that statins interfere with the formation of ubiquinone (also called coenzyme Q10), a byproduct of cholesterol synthesis. Since ubiquinone plays an important role in the cellular energy transduction of the mitochondrial electron transport system, decreased levels of ubiquinone may cause myotoxicity.[73] The other risk factors for the occurrence of muscle toxicity are increasing dose, advanced age, female gender, hepatic dysfunction, hypothyroidism, and concurrent use of agents such as cytochrome P450 inhibitors, azole antifungals, Fibrates and niacin etc. Thus statins should be discontinued in patients who develop intolerable muscle symptoms. [74]

DRUG PROFILE-I

ATORVASTATIN CALCIUM

BRAND NAME: Storvas, Lipitor

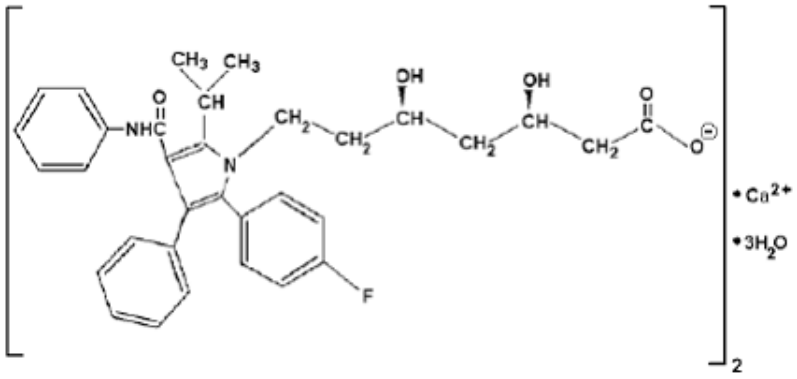
CHEMICAL NAME:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate.

EMPIRICAL FORMULA: $(C_{33}H_{34}FN_2O_5)2Ca•3H_2O$

MOLECULAR WEIGHT is 1209.42.

STRUCTURAL FORMULA:



DESCRIPTION

Storvas is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol and freely soluble in methanol.

CLINICAL PHARMACOLOGY

Mechanism of action:

STORVAS (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, rate-limiting step in the biosynthesis of cholesterol. It lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).It also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

PHARMACOKINETICS

Absorption:

Atorvastatin is rapidly absorbed after oral administration, maximal plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95-99% bioavailable compared to solutions. The absolute bioavailability (parent drug) of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and first-pass metabolism in the liver.

Distribution:

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is 98% bound to plasma proteins.

Metabolism:

Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives by cytochrome P-450 3A4 (CYP 3A4) and to various β-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion:

Atorvastatin is eliminated primarily in bile following hepatic and or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life for inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

DOSAGE FORMS:

Tablets are formulated for oral administration and are available in tablet doses of 10 mg, 20 mg, 40 mg and 80 mg.

INDICATION:

Adjunct to lifestyle changes, including diet, for the reduction of elevated total cholesterol (total-C), LDL-C, triglycerides (TG), apolipoprotein B (apo B), the Total-C/HDL-D ratio and for increasing HDL-C in hyperlipidemic and dyslipidemic conditions.

CONTRAINDICATIONS & PRECAUTIONS:

Contraindicated in patient's hypertensive to drug with Active liver disease, unexplained persistent elevations of serum transaminase levels, in pregnant or breast feeding women and in women of child bearing. Use cautiously in patients with history of hepatic disorder and heavy alcohol use.

SPECIAL POPULATIONS:

Pediatrics:

Pharmacokinetic data in the pediatric population are not available.

Geriatrics:

Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age 65 years or older) compared with younger individuals. LDL-C reduction, however, is comparable to that seen in younger patient populations.

Gender:

Plasma concentrations of atorvastatin in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men, however, there is no clinically significant difference in LDL-C reduction between men and women.

Race:

Plasma concentrations of atorvastatin are similar in black and white subjects.

Hepatic Insufficiency:

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease.

DRUG INTERACTIONS:

- **Strong Inhibitors of CYP 3A4**

Atorvastatin calcium is metabolized by cytochrome P450 3A4. Concomitant administration of Atorvastatin calcium with strong inhibitors of CYP3A4 (clarithromycin, HIV protease inhibitors, and itraconazole) can lead to increase in plasma concentrations of atorvastatin.

- **Grapefruit Juice**

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (> 1.2 liters per day).

- **Digoxin**

Plasma digoxin concentrations increased by approximately 20%.

STORAGE:

Store at controlled room temperature 15 to 30ºC.

DRUG PROFILE-II

SIMVASTATIN

BRAND NAME: ZOCOR

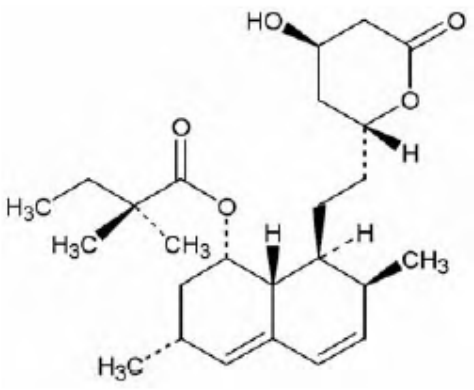
CHEMICAL NAME

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8aβ]].

EMPIRICAL FORMULA: $C_{25}H_{38}O_5$

MOLECULAR WEIGHT : 418.57

STRUCTURAL FORMULA:



DESCRIPTION

ZOCOR (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin which is an inactive lactone is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Simvastatin is a white to off-white, non-hygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

CLINICAL PHARMACOLOGY

Mechanism of action:

Simvastatin is a prodrug and is hydrolyzed to its active hydroxyacid, simvastatin acid form. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

PHARMACOKINETICS

Absorption:

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

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Distribution:

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins.

Metabolism:

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours post dose.

Excretion:

Following an oral dose, 13% of the dose was excreted in urine and 60% in faeces.

DOSAGE FORMS:

The usual dosage range is 5 to 40 mg/day.

INDICATIONS:

Adjunct to lifestyle changes, including diet, for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia.

CONTRAINDICATIONS & PRECAUTIONS

Contraindicated in patient's hypertensive to drug with Active liver disease, unexplained persistent elevations of serum transaminase levels, in pregnant or breast feeding women and in women of child bearing.

SPECIAL POPULATIONS

Pediatrics:

Simvastatin has not been studied in patients younger than 10 years of age, or in pre-menarcheal girls.

Geriatrics:

Since advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, Zocor should be prescribed with caution in the elderly.

Hepatic Impairment:

Zocor is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels.

DRUG INTERACTIONS

Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily).

The combined use of simvastatin with gemfibrozil, cyclosporine, or danazol is contraindicated as these agents can cause myopathy when given alone and the risk is increased when they are co-administered.

STORAGE:

Store at controlled room temperature 5 to 30ºC.

REVIEW OF LITERATURE

- **Jason. P. Swindle, et al[75].,** examined differences in drug utilization and CV event risk among elderly patients newly initiated on simvastatin versus atorvastatin. Enrollees aged ≥65 years, newly initiated on simvastatin or Atorvastatin from July 1, 2006 to November 30, 2008 were identified for study inclusion. Patients were excluded if they had any prescriptions for clopidogrel, nitrates, or other dyslipidemia medication, or any CV events before index drug initiation. Adherence was calculated by proportion of days covered with index medication. The majority of patients started on low-dose therapy and did not achieve sufficient adherence. After controlling for patient and clinical characteristics, no statistically significant difference in risk of CV event was observed based on initiation with atorvastatin versus simvastatin.

- **Jennifer. G. Robinson, et al[76].,** assessed percent change from baseline in lipids and high-sensitivity C-reactive protein (hs-CRP) levels and the proportion of subjects reaching specified low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (Apo B). Adults (N = 1143) with Metabolic syndrome and hypercholesterolemia were randomized to starting and next higher doses of ezetimibe/simvastatin (10/20 or 10/40 mg) or atorvastatin (10, 20, or 40 mg). More intensive therapy was required for >80% of subjects to achieve LDL-C <100 mg/dL and non-HDL-C <130 mg/dL and for the majority of subjects to achieve lower levels of LDL-C <70 mg/dL, non-HDL-C <100 mg/dL, and/or Apo B <90 mg/dL. The effect of ezetimibe on cardiovascular risk reduction has yet to be established.

- **Amy Furman, et al[77].,** carried out a Retrospective study in Veterans Affairs Health Care System over a 3-year time period. The primary objective of this study was to determine the LDL-lowering efficacy of higher-potency strategies (ezetimibe/simvastatin, rosuvastatin, and atorvastatin) in high-risk patients who were switched from simvastatin therapy. Secondary objectives were to evaluate patient adherence to these therapies, determine the efficacy of these interventions on other lipid parameters, and define the incidence of adverse effects. Lipid data were assessed prior to and within 2 to 6 months following the conversion from

simvastatin. Adherence to therapy was determined by medication refill data. At the doses used in this population, ezetimibe/simvastatin resulted in greater LDL reductions than rosuvastatin or atorvastatin. The clinical impact of these differences is as yet undetermined.

- **James McKenney, et al[78].,** compared the proportion of patients at high risk for coronary heart disease (CHD) achieving the recommended low-density lipoprotein cholesterol (LDL-C) treatment goal of < 100 mg/dL and the optional LDL-C target of < 70 mg/dL with co administration of ezetimibe and simvastatin (EZE/SIMVA) Vs either atorvastatin or simvastatin monotherapy. Patients at high risk for CHD are more likely to attain LDL-C treatment targets with the usual recommended starting dose of EZE/SIMVA (10 or 20 mg) therapy than with that of atorvastatin (10 mg) or simvastatin (20 mg) monotherapy.

- **Samir Maruti Adsule, et al[79].,** evaluated and compared the safety and efficacy of rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes mellitus with Dyslipidemia. This open-label, randomized, parallel group, comparative, prospective study of 12-weeks duration included 60 patients of type-2 diabetes with Dyslipidemia having good glycemic control with fixed dose combination of tablet glimepiride + metformin and divided into three groups of twenty each. 10 mg of rosuvastatin was comparable to 10 mg of atorvastatin and more efficacious than 10 mg simvastatin in reducing LDL levels after 12 weeks of therapy in patients of type 2 diabetes mellitus with Dyslipidemia.

- **William Insull Junior, et al[80].,** compared the efficacy and safety of a proprietary niacin extended-release and simvastatin (NER/S) combination to atorvastatin monotherapy in a multicenter, Prospective, Randomized (3:2), Open-label, Blinded Endpoint (PROBE) study. Following ≥4 weeks without lipid-modifying therapies, 193 patients with dyslipidemia were treated with NER/S (n = 114; 1000/40 mg/day, weeks 1 to 4; 2000/40 mg/day weeks 5 to 12) or atorvastatin (n = 79; 40 mg/day, weeks 1 to 12). Compared to atorvastatin, NER/S provided superior improvements in HDL-C, TG, and Lp (a) and comparable improvements in non-HDL-C and LDL-C. Treatment with NER/S should be considered for patients with dyslipidemia requiring comprehensive lipid control.

- **Suyog Sindhu, et al[81].,** evaluated and compared the effects on high-sensitivity C-reactive protein (hs-CRP) levels and lipid profile of atorvastatin and rosuvastatin in obese type 2 diabetes mellitus (T2DM) patients. Results obtained from the study, clearly indicate that atorvastatin (A) as well as rosuvastatin(R) have significant effect on lowering of hs-CRP levels (for A p=0.001; for R p=0.002), reducing LDL-C levels (for A p=0.008; for R p=0.001), elevating HDL-C levels (for A p=0.02; for R p=0.001) along with reducing TC (for A p=0.003; for R p=0.002) and TG (for A p=0.000; for R p=0.000) levels in obese T2DM patients. It is also seen that there is no significant (p>0.05) difference in effect of atorvastatin and rosuvastatin lowering of hs-CRP levels, elevating HDL-C levels and reducing TG levels in obese T2DM patients. Thus this study throws light on the fact that rosuvastatin should be preferred over atorvastatin in obese T2DM patients in whom LDL-C and TC levels are deviated from normal reference values.

- **Dagmar Vondrakova, et al[82].,** analyzed a group of 114 patients with ACS (mean age 63.7; females 25.4%). Atorvastatin 80 mg was administered at admission and then once daily for the rest of hospitalization. The levels of total cholesterol (TC), LDL-cholesterol (LDL), HDL-cholesterol (HDL), and triglycerides (TG) were measured at admission (D0), and then every morning of hospitalization (D1, D2).It is shown that ACS patients has a highly significant, immediate effect on all monitored lipid levels. Since TC and LDL levels were decreased as predicted, reduction in HDL and increase in TG levels suggest a different acute effect of high-dose statin on lipid levels in comparison with long-term treatment of ACS patients.

- **Jong-Seon Park, et al[83].,** compared the effects of rosuvastatin 10 mg and atorvastatin 10 mg on lipid and glycemic control in Korean patients with nondiabetic metabolic syndrome. This was a multicenter, open-labeled, randomized trial performed on 351 patients who met the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for metabolic syndrome with low-density lipoprotein cholesterol (LDL-C) levels > or = 130 mg/dL were randomized to receive either rosuvastatin 10 mg (n = 173) or atorvastatin 10 mg (n = 178) for over 6 weeks. It was found that Rosuvastatin 10 mg was more effective than atorvastatin 10 mg in achieving NCEP ATP III LDL-C

goals in patients with nondiabetic metabolic syndrome, especially in those with lower NCEP ATP III target level goals.

- **Beth L Abramson, et al[84].,** conducted a study in which Data were combined from 27 double-blind, active or placebo-controlled studies that randomized adult hypercholesterolemic patients to statin or statin+ezetimibe. Consistency of treatment effect among men (n = 11,295) and women (n = 10,499) was assessed and percent of men and women was calculated to evaluate the between-treatment ability to achieve specified treatment levels between sexes. The results suggest that small sex-related differences may exist in response to lipid-lowering treatment and achievement of specified lipid and hs-CRP levels, which may have implications when managing hypercholesterolemia in women.

- **Larry B. Goldstein, et al[85].,** conducted a randomized trial which is designed to determine whether treatment with atorvastatin reduces strokes in subjects with recent stroke or transient ischemic attack (n=4731). Severity was assessed with the National Institutes of Health Stroke Scale, Barthel Index, and modified Rankin Scale score at enrollment (1 to 6 months after the index event) and 90 days poststroke in subjects having a stroke during the trial. This study suggests that the outcome of recurrent ischemic cerebrovascular events might be improved among statin users as compared with nonusers.

- **Kuan Gandelman, et al[86].**, assessed the efficacy and tolerability of atorvastatin in Tanner stage (TS) 1 patients ages 6 to 10 years and TS ≥ 2 patients ages 10 to <18 years with genetically confirmed heterozygous familial hypercholesterolemia (HeFH) and a low density lipoprotein cholesterol (LDL-C) level of 4 mmol/l (155 mg/dL) or higher. This study suggests tat there was no difference in safety or tolerability was observed between the younger and older cohorts. Across the range of exposures after atorvastatin 5 to 10 mg (TS 1) or atorvastatin 10 to 20 mg (TS ≥ 2) doses for 8 weeks, clinically meaningful reductions in LDL-C, TC, VLDL-C, and Apo were observed with atorvastatin in pediatric patients who had HeFH. Atorvastatin also was well tolerated in this population.

- **Eyal Leibovitz, et al[87].,** had evaluated the effect of atorvastatin on plasma fibrinogen levels in patients with severe hypercholesterolemia and no other risk factors. Twenty-two patients with low density lipoprotein-cholesterol levels above 170 mg/dl (4.40mmol/L) and with no other risk factors were included in the study. After 24 weeks of follow-up, total cholesterol decreased by 33% (287 +/- 10 to 192 +/- 8 mg/dl, P < 0.001), LDL-C by 45% (198 +/- 8 to 111 +/- 7 mg/dl, p < 0.001) and triglycerides by 21% (189 +/- 26 to 138 +/- 15 mg/dl, P < 0.001). Fibrinogen levels dropped by 18% (355 +/- 26 to 275 +/- 7 mg/dl, P = 0.01). CRP levels decreased from 0.51 +/- 0.15 to 0.28 +/- 0.10 mg/dl, but the difference was not statistically significant (P = 0.09). High density lipoprotein, hemoglobin, white blood cell and platelet counts did not change.

- **Gianluca Bardini, et al[88].,** performed a randomized, double-blind, double-dummy study in patients with type 2 diabetes mellitus (T2DM). Adult patients with T2DM and CHD (N = 93) on a stable dose of simvastatin 20 mg with LDL-C >or= 2.6 mmol/L (100 mg/dL) and <or= 4.1 mmol/L (160 mg/dL) were randomized to ezetimibe 10 mg plus simvastatin 20 mg (EZ + simva 10/20 mg) or simvastatin 40 mg for 6 weeks. Percent change in LDL-C, high-density lipoprotein cholesterol, and triglyceride was assessed. The results demonstrate that EZ + simvastatin 10/20 mg may provide a superior alternative for LDL-C lowering Vs doubling the dose of simvastatin to 40 mg in hyperlipidemic patients with T2DM and CHD. In addition, the combination therapy may provide an alternative treatment for patients who require further LDL-C reduction than they can achieve with simvastatin 20 mg alone.

- **John J.P. Kastelein, et al[89].,** conducted a double-blind, randomized, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in 720 patients with familial hypercholesterolemia. Patients underwent B-mode ultrasonography to assess the intima-media thickness of the walls of the carotid and femoral arteries. The primary outcome measured was the change in the mean carotid-artery intima-media thickness. In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes

in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein.

- **Michel Farnier, et al[90].,** explored the frequency/magnitude of HDL-C reductions in a pooled database of mixed dyslipidemic patients (LDL-C: 3.4-5.7 mmol/L;TG:1.7-5.7 mmol/L) receiving placebo (PBO), fenofibrate (FENO), ezetimibe plus FENO (EZE+FENO), or EZE/simvastatin plus FENO (EZE/SIMVA+FENO) for 12 weeks. PBO-treated patients had the highest incidence of HDL-C reductions from baseline (45%) compared with patients taking FENO (14%), EZE+FENO (9%), or EZE/SIMVA+FENO (9%). The incidence of paradoxical HDL-C reductions was low in mixed dyslipidemic patients receiving FENO alone or combined with EZE or EZE/SIMVA.

- **Dong Kyun Kim, et al [91].,** carried out a retrospective study to evaluate the efficacy of 10 mg dosage of atorvastatin in a clinical setting. One hundred five enrolled patients with high levels of low density lipoprotein cholesterol (LDL-C, > 100 mg/dL) took 10 mg atorvastatin. After 6 months, they were divided into Responder group (LDL-C < 100 mg/dL) and Non-responder group (LDL-C ≥ 100 mg/dL), and the response rate was calculated. Thereafter, we subdivided the Responder group into Maintenance (10 mg), Reduced dosage (5 mg), and Discontinuance group (0 mg). The Non-Responder group was subdivided into Maintenance (10 mg) and Double dosage group (20 mg). After consecutive 6 months, the response rates of each 10 mg Maintenance groups were compared to those of the other groups, respectively. Hypercholesterolemia treatment with 10 mg, fixed dosage of atorvastatin was effective in three quarters of the subjects during the first 6-month treatment; however, a significant number of patients with high LDL-C levels and/or BMI require higher starting and maintenance dosage.

- **Thozhukat Sathyapalan, et al[92].**, compared the effect of equivalent LDL-lowering doses of simvastatin and atorvastatin on hsCRP in type 2 diabetic patients. A crossover study of 26 patients with type 2 diabetes taking either 40mg simvastatin or 10 mg atorvastatin was undertaken. After 3 months on one statin, lipids and hsCRP were measured on 10 occasions over a 5-week period. The same procedure was then followed taking the other statin. The results showed that

compared with simvastatin, atorvastatin reduced hsCRP and its variability in type 2 diabetic patients.

- **Carlo M Rotella, et al[93].,** conducted a randomized double blind study. After stabilization on simvastatin 20 mg, patients with coronary heart disease (CHD) alone and/or type 2 diabetes mellitus (T2DM) were randomized to ezetimibe 10 mg/simvastatin 20 mg (EZ/Simva) or simvastatin 40 mg. EZ/Simva treatment (N = 93) resulted in significantly greater reductions in LDL-C, TC, and TC/HDL-C ratio and higher attainment of LDL-C < 2.6 mmol/L Vs doubling the simvastatin dose to 40 mg (N = 106). Study [including diabetic patients (OR = 2.9, p = 0.003)], EZ/Simva treatment (OR = 6.1, p < 0.001), and lower baseline LDL-C (OR = 0.9, p = 0.001) were significant positive predictors of LDL-C target achievement. When baseline LDL-C was expressed as a discrete variable, the odds of achieving LDL-C < 2.6 mmol/L was 4.8 in favor of EZ/Simva compared with Simva 40 mg (p < 0.001), regardless of baseline LDL-C level. EZ/Simva is an effective therapeutic option for patients who have not achieved recommended LDL-C treatment targets with simvastatin 20 mg monotherapy.

- **G**. **Avellone, et al[94].**, conducted a 1-year open-label study to test the efficacy and tolerability of Atorvastatin titrated to the target, in proven FH patients and to evaluate certain inflammatory parameters. One hundred and two FH patients (44 men and 58 women; mean age 58.7+/-3.6 years) were included in the study. After evaluation using the B-mode duplex scanning system of extracranial carotid arteries, the patients were divided into two groups: Group 1 (15 men, 25 women) with carotid plaques or intima-media thickness (IMT) greater than 0.95 mm and Group 2 (30 men, 32 women) without carotid plaques or IMT less than 0.95 mm. After a 6-week hypolipemic diet phase all the patients were treated with atorvastatin titrated to achieve a low density lipoprotein (LDL-C) <100 mg/dL. Patients with carotid lesions were also submitted to an oral fixed dose of aspirin 100 mg/day. In FH patients, 1-year atorvastatin treatment titrated to the target (LDL-C <100 mg/dL) was well tolerated and improved serum lipid levels and inflammatory parameters.

- **Jones P. H, et al[95].,** examined prospectively the effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin across dose ranges on non-HDL-C, apo B, apo A-I, and total cholesterol (TC):HDL-C, low-density lipoprotein cholesterol (LDL-C):HDL-C, non-HDL-C:HDL-C, and apoB:apoA-I ratios in patients with hypercholesterolemia (LDL-C > or =160 mg/dL and <250 mg/dL and triglycerides <400 mg/dL) in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial. Rosuvastatin 10 to 40 mg was more efficacious in improving the lipid profile of patients with hypercholesterolemia than milligram-equivalent doses of atorvastatin and milligram-equivalent or higher doses of simvastatin and pravastatin.

- **Roxanne A. Rodney, et al[96].,** examined the efficacy and safety of ezetimibe (EZE) co administered with simvastatin (SIMVA) in a large cohort of African Americans with primary hypercholesterolemia. Eligible patients were randomized to SIMVA 20 mg co administered with either EZE 10 mg (n = 124) or placebo (n = 123) for 12 weeks. At study endpoint, EZE/SIMVA 10/20 mg resulted in a significant mean percent reduction in LDL cholesterol from baseline of 45.6% compared with 28.3% for SIMVA 20 mg alone ($p < or = 0.01$). There were significantly greater mean reductions in total cholesterol (33% vs. 21%), triglycerides (median 22% vs. 15%), nonhigh-density-lipoprotein (non-HDL) cholesterol (42% vs. 26%), and apolipoprotein B (38% vs. 25%) with EZE/SIMVA 10/20 mg compared with SIMVA 20 mg alone, respectively ($p < or = 0.01$). Co administration of EZE/SIMVA 10/20 mg demonstrated a safety profile similar to that of SIMVA 20 mg. In conclusion, EZE/SIMVA 10/20 mg provided significantly greater improvement in atherogenic lipid profiles and was well tolerated compared with SIMVA 20-mg monotherapy in a large cohort of African Americans with primary hypercholesterolemia.

- **William Insull Jr, et al[97].**, compared the effects of combination niacin extended-release + simvastatin (NER/S) versus atorvastatin alone on apolipoproteins and lipid fractions in a post hoc analysis from SUPREME, a study which compared the lipid effects of niacin extended-release + simvastatin and atorvastatin in patients with hyperlipidemia or mixed dyslipidemia. NER/S treatment significantly improved apo A-I levels and the apo B:A-I ratio, significantly lowered the number

of atherogenic LDL particles and VLDL and chylomicron particles, and increased the mean size of LDL and VLDL particles, compared with atorvastatin.

- **F. van Nooten, et al[98].,** aimed to assess the cost-effectiveness of ezetimibe plus simvastatin (E/S) versus atorvastatin or simvastatin monotherapy as second-line treatment of primary hypercholesterolemia from the Dutch healthcare perspective. The analysis showed the cost-effectiveness of E/S versus atorvastatin 20 mg or simvastatin 40 mg (EASEGO scenario) at a threshold of <euro>30,000/QALY and vs atorvastatin 40 mg was dominant (Dutch guidelines).Thus, E/S seems a valuable cost-effective second-line treatment option for patients not attaining lipid treatment goals.

- **Yun-Kyeong Cho, et al[99].,** compared the effect of ezetimibe/simvastatin 10/20 mg and atorvastatin 20 mg on achieving a target LDL-C goal in very high risk patients. Baseline clinical and laboratory data were similar between the two groups. Achieving a target LDL-C goal was observed in 41.7% of Group 1 and 44.7% of Group 2 at 6 weeks (p=0.82). Changes in other lipid profiles were not significantly different but the tolerability of the two groups was similar. Ezetimibe/simvastatin 10/20 mg and atorvastatin 20 mg showed similar effects in achieving target LDL-C levels in patients with very high risk.

- **Tatjana Abel, et al[100].,** determined the efficacy and safety of ezetimibe/ simvastatin 10/20mg combination therapy on patients with type 2 diabetes and nonalcoholic fatty liver disease. Six months of ezetimibe/ simvastatin administration reduced significantly the serum levels of ALT (63.78+/-5.12 vs 32.57+/-3.92 U/L; $p < 0.0001$), AST (50.79+/-3.66 vs 23.68+/-3.42 U/L; $p < 0.0001$), cholesterol (6.26+/-0.46 vs 4.02+/-0.31 mmol/L; $p < 0.0001$) and LDL-cholesterol (4.24+/-0.37 vs 2.22+/-0,1 mmol/L; $p < 0.0001$). Combination therapy reduced significantly serum triglyceride level (2.62+0.48 vs 1.33+0.20 mmol/L; $p < 0.0001$) and increased the level of HDL-cholesterol (1.02+/-0.12 vs 1.18+ /-0.07 mmol/L; $p < 0.0001$). These findings indicate that ezetimibe/ simvastatin combination therapy is safe and effective in patients with type 2 diabetes and nonalcoholic fatty liver disease.

- **Kazuo Nakamura, et al[101].,** conducted a study to compare the effects of atorvastatin plus aspirin combined therapy on inflammatory responses, endothelial cell function, and blood coagulation system in patients undergoing coronary artery bypass grafting (CABG) to aspirin monotherapy. The patients were randomized into atorvastatin plus aspirin combined therapy group and aspirin monotherapy group. Reduced total cholesterol in the combined therapy group was found in a short term of medication for 14 days. On postoperative day (POD)-14, inhibitory effects of the combined therapy on whole blood aggregation as well as platelet activation assessed by flow cytometry were stronger than those of the monotherapy. In conclusion, atorvastatin and aspirin combined therapy may bring beneficial effects to the patient after CABG.

- **Nicola Abate, et al[102].,** compared the effects of ezetimibe/simvastatin (E/S) combination therapy, atorvastatin, and rosuvastatin in patients with DM, MS without DM, or neither disease. Treatments were compared by pooling across all doses for effects on low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), non–HDL-C, apolipoprotein B (ApoB), LDL-C:HDL-C, TC:HDL-C, and LDL-C goal attainment. In conclusion, E/S generally provided greater efficacy than either atorvastatin or rosuvastatin that was consistent across the subgroups of patients with DM, MS.

- **Joanna M. Young, et al[103].,** evaluated the effect of coenzyme Q10 supplementation on statin tolerance and myalgia in patients with previous statin related myalgia. Forty-four patients were randomized to coenzyme Q10 (200 mg/day) or placebo for 12 weeks in combination with upward dose titration of simvastatin from 10 mg/day, doubling every 4 weeks if tolerated to a maximum of 40 mg/day. Patients experiencing significant myalgia reduced their statin dose or discontinued treatment. Myalgia was assessed using a visual analogue scale**.** In conclusion, coenzyme Q10 supplementation did not improve statin tolerance or myalgia, although further studies are warranted.

- **Sophie L. Rogers, et al[104].,** conducted meta-analyses to assess the relative potency of atorvastatin and simvastatin across all possible dose combinations in terms of changes in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). Seventeen published trials and 1 unpublished study were included in the meta-analyses. It was found that atorvastatin was 2 to 4 times as potent as simvastatin in reducing TC, LDL-C, and TG, indicating that the dose equivalence of atorvastatin and simvastatin lay between 1: 2 and 1:4. In contrast, simvastatin was more effective than atorvastatin in increasing HDL-C, but without any indication of a point of dose equivalence.

- **Matthew A. Silva, et al[105].,** conducted a meta-analysis study intended to synthesize the collective AE data observed in prospective randomized clinical trials to facilitate clinical interpretation. The MEDLINE/EMBASE and the Cochrane Collaboration databases were reviewed for prospective randomized primary and secondary prevention trials of statin monotherapy. Nonrandomized uncontrolled studies and those missing AE data were excluded. Statin therapy was associated with greater odds of AEs compared with placebo but with substantial clinical benefit. Similar rates of serious AEs were observed between statin and placebo.

AIM AND OBJECTIVES

AIM:

The aim of the study is a "comparative evaluation of the efficacy and side effect profile of Simvastatin versus Atorvastatin in Dyslipidemic Patients".

OBJECTIVES:

- To assess the lipid profile of patients before and after drug administration.
- To study the association of lipid profile and various demographic, clinical and personal habits(like age, gender, hypertension, diabetes mellitus, coronary artery disease, alcoholic, smoking and family history) in patients receiving Simvastatin and Atorvastatin.
- To study the side effects if any, associated with drug intake in the above groups.

PLAN OF WORK

The Proposed plan of the work is to compare the efficacy and side effect profile of Simvastatin versus Atorvastatin in Dyslipidemic Patients.

- Collection of Dyslipidemic Patients.
- Documentation of case History to find out the number of patients who has elevated levels of Total Cholesterol, Triglycerides, Low density Lipoprotein, and decreased levels of High Density Lipoprotein.
- Assess the side effect profile of each patient during the study.
- Analyze the collected Data.
- Interpreting the data into statistical inference using statistical tools.
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OBSERVATIONS AND RESULTS

COMPARISON OF A20 WITH A40

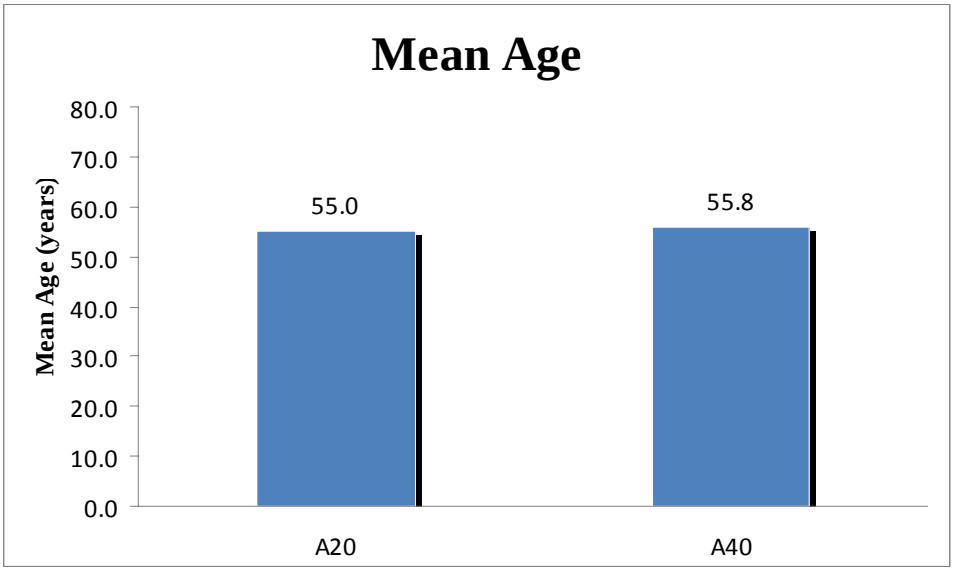
1. Comparison of Age between A20 and A40

Table No: 7 Age Distribution

Drug	Mean	Std. Deviation	P value
A20 (Atorvastatin 20)	**55.03**	**10.220**	**0.769**
A40 (Atorvastatin 40)	**55.83**	**10.751**	

When chi square test was done, p value was 0.769. So, there was no statistically significant difference between age distribution and the two study groups and the graphical representation is shown in Fig No: 2

Fig No: 2



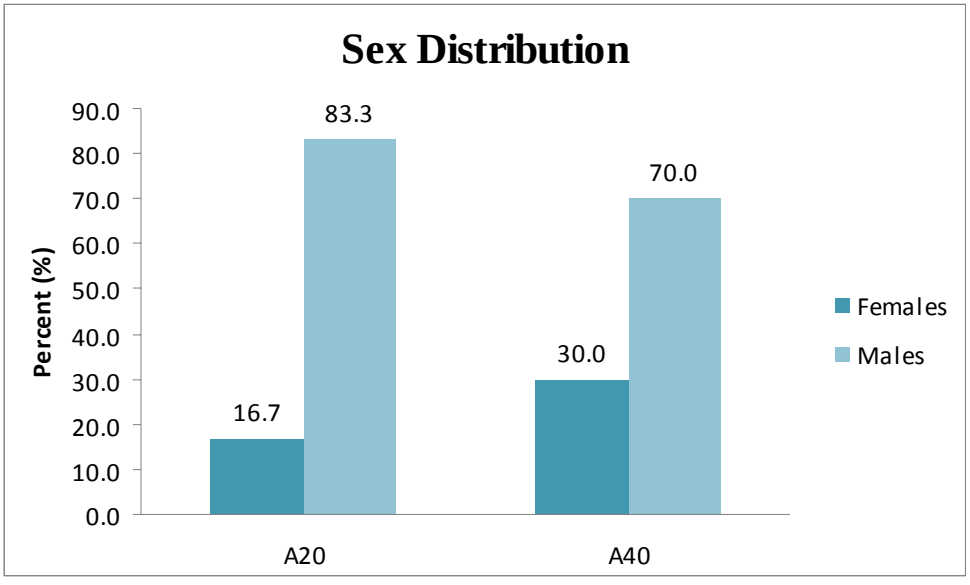
2. Comparison of Sex Distribution between A20 and A40

Table No: 8 Sex Distribution

Sex Distribution		Drug		p value
		A20 (Atorvastatin 20)	A40 (Atorvastatin 40)	
Female	No: of patients	5	9	0.222
	Percentage of patients	16.7%	30.0%	
Male	No: of patients	25	21	
	Percentage of patients	83.3%	70.0%	

When Pearson chi square test was done, p value was 0.222. So, there was no statistically significant difference between sex and the two study groups and the graphical representation is shown in Fig No: 3

Fig No: 3



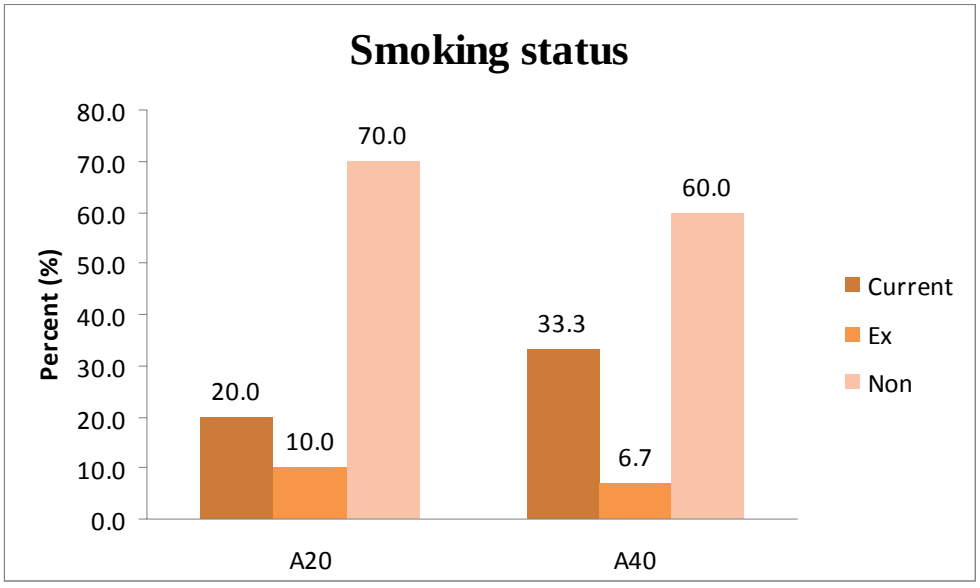
3. Comparison of Smoking between A20 and A40

Table No: 9 Smoking Status

Smoking		Drug	
		A20 (Atorvastatin 20)	A40 (Atorvastatin 40)
Current-Smoker	No: of patients	6	10
	Percentage of patients	20.0%	33.3%
Ex-Smoker	No: of patients	3	2
	Percentage of patients	10.0%	6.7%
Non Smoker	No: of patients	21	18
	Percentage of patients	70.0%	60.0%

Statistical analysis using Fisher's Exact Test shows that p value is 1.000. Hence statistically it is not significant and the graphical representation is shown in Fig No: 4

Fig No: 4



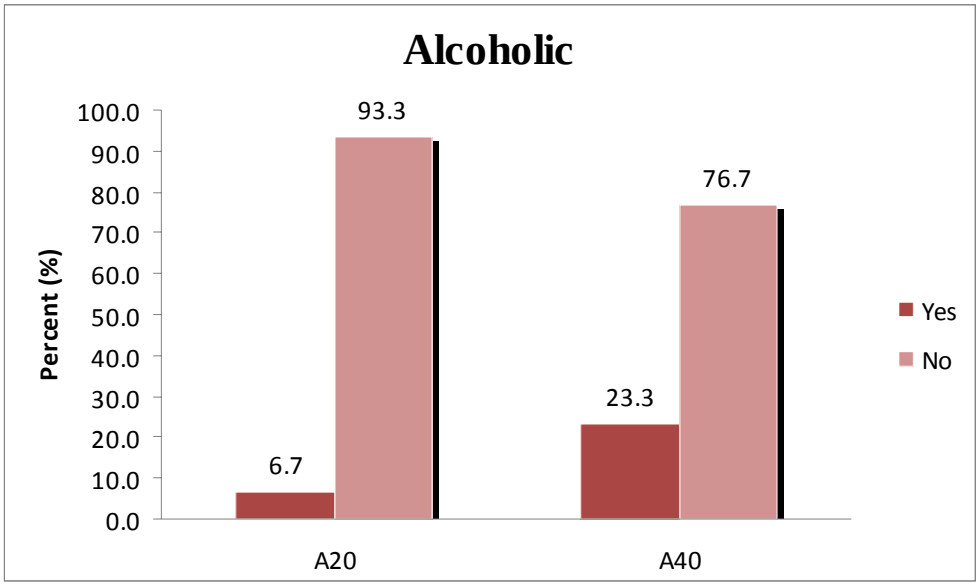
4. Comparison of Alcoholics between A20 and A40

Table No: 10 Alcoholics

Alcoholic		Drug	
		A20 (Atorvastatin 20)	**A40 (Atorvastatin 40)**
Present	**No: of patients**	**2**	**7**
	Percentage of patients	**6.7%**	**23.3%**
Absent	**No: of patients**	**28**	**23**
	Percentage of patients	**93.3%**	**76.7%**

Statistical analysis using Fisher's Exact Test shows that p value is 0.145. Hence statistically it is not significant and the graphical representation is shown in Fig No: 5

Fig No: 5



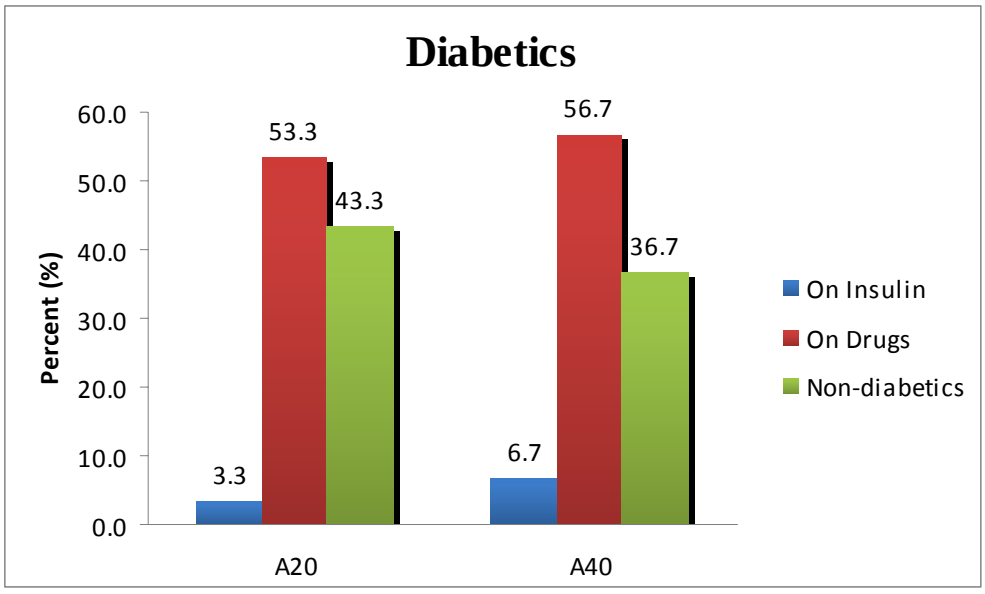
5. Comparison of Diabetes between A20 and A40

Table No: 11 Diabetes Mellitus

Diabetics		Drug	
		A20 (Atorvastatin 20)	A40 (Atorvastatin 40)
On Insulin	No: of patients	1	2
	Percentage of patients	3.3%	6.7%
On Drugs	No: of patients	16	17
	Percentage of patients	53.3%	56.7%
Non Diabetic	No: of patients	13	11
	Percentage of patients	43.4%	36.6%

Statistical analysis using Fisher's Exact Test shows that p value is 1.000. Hence statistically it is not significant and the graphical representation is shown in Fig No: 6

Fig No: 6



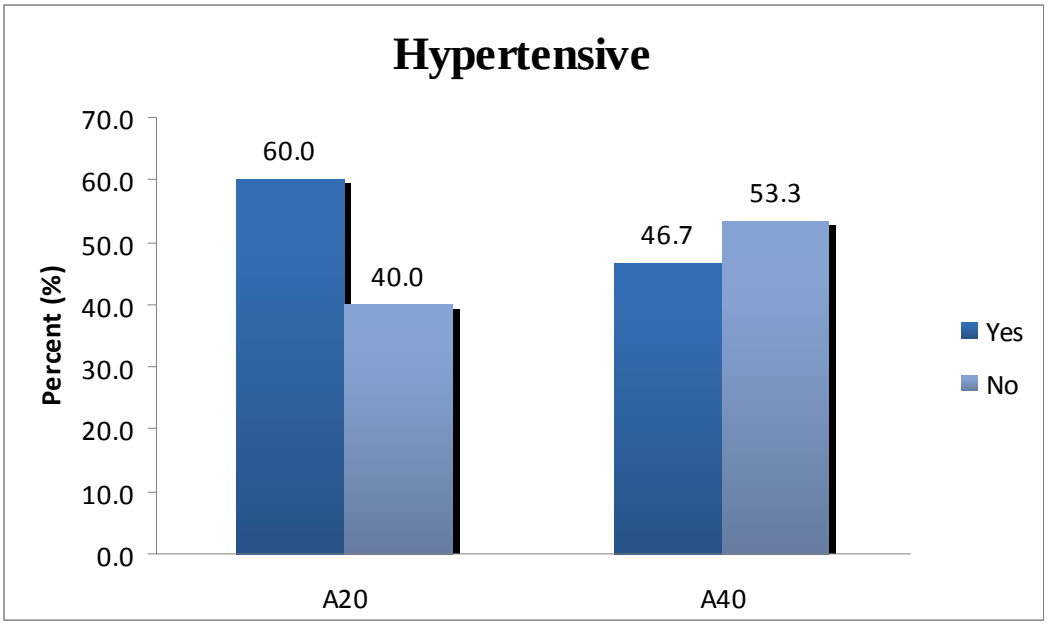
6. Comparison of Hypertension between A20 and A40

Table No: 12 Hypertension

Hypertension		Drug	
		A20 (Atorvastatin 20)	A40 (Atorvastatin 40)
Hypertensive	No: of patients	18	14
	Percentage of patients	60.0%	46.7%
Normotensive	No: of patients	12	16
	Percentage of patients	40.0%	53.3%

Statistical analysis using Pearson Chi-Square shows that p value is 0.301. Hence statistically it is not significant and the graphical representation is shown in Fig No: 7

Fig No: 7



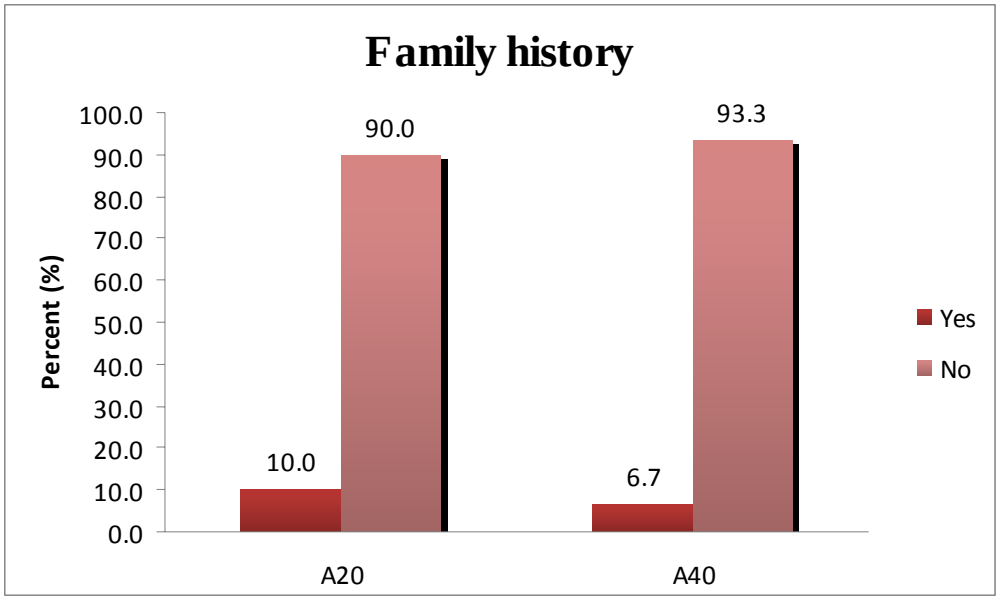
7. Comparison of Family History between A20 and A40

Table No: 13 Family History

Family History		Drug	
		A20 (Atorvastatin 20)	A40 (Atorvastatin 40)
Present	No: of patients	3	2
	Percentage of patients	10.0%	6.7%
Absent	No: of patients	27	28
	Percentage of patients	90.0%	93.3%

Statistical analysis using Fisher's Exact Test shows that p value is 1.000. Hence statistically it is not significant and the graphical representation is shown in Figure. 8

Fig No: 8



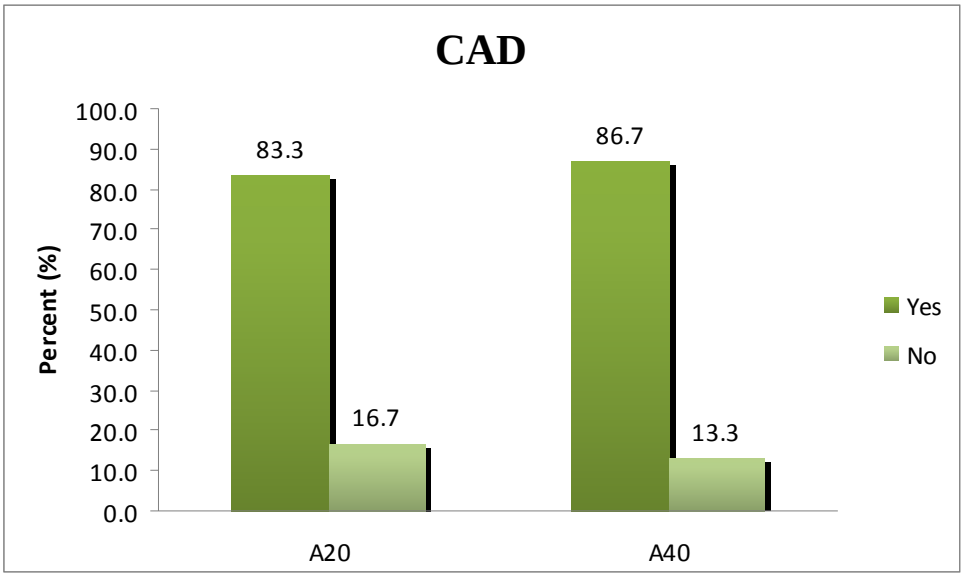
8. **Comparison of Cardiovascular events between A20 and A40**

Table No: 14 Cardiovascular events

CAD		Drug	
		A20 (Atorvastatin 20)	**A40 (Atorvastatin 40)**
Present	**No: of patients**	**25**	**26**
	Percentage of patients	**83.3%**	**86.7%**
Absent	**No: of patients**	**5**	**4**
	Percentage of patients	**16.7%**	**13.3%**

Statistical analysis using Fisher's Exact Test shows that p value is 1.000. Hence statistically it is not significant and the graphical representation is shown in Fig No: 9

Fig No: 9



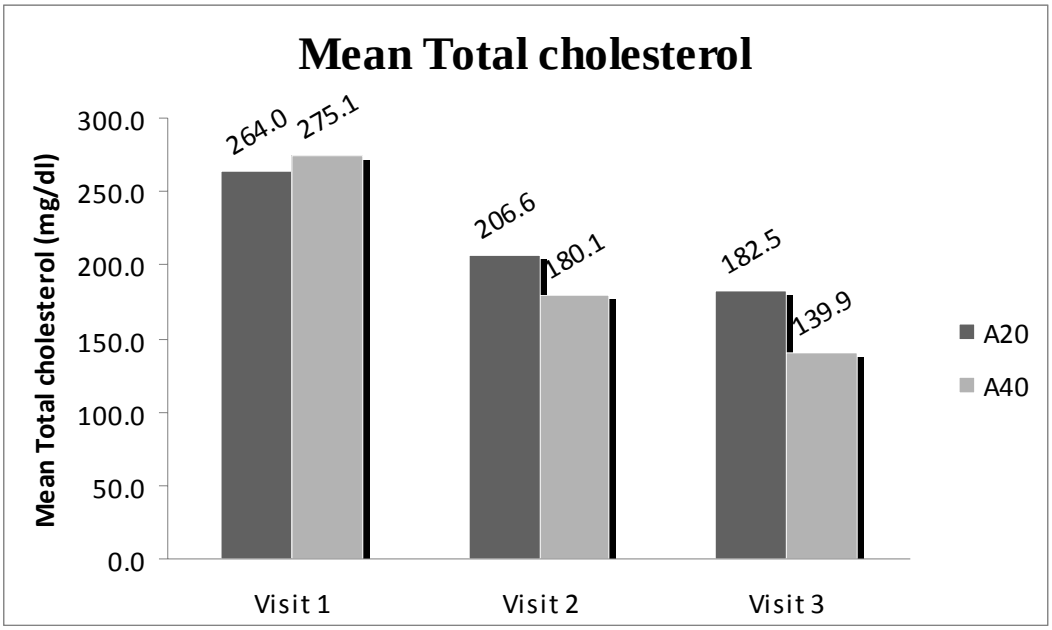
9. Comparison of Total Cholesterol between A20 and A40

Table No: 15 Total Cholesterol

Drug		Visit 1	Visit 2	Visit 3	p value
A20 (Atorvastatin 20)	Mean	264.00	206.57	182.47	<0.05
	Std. Deviation	31.414	29.600	22.332	
A40 (Atorvastatin 40)	Mean	275.10	180.07	139.90	
	Std. Deviation	27.353	30.674	19.090	

When chi square test was done, p value was <0.05. So, the comparison of total cholesterol was found to be statistically significant and the graphical representation is shown in Fig No: 10

Fig No: 10



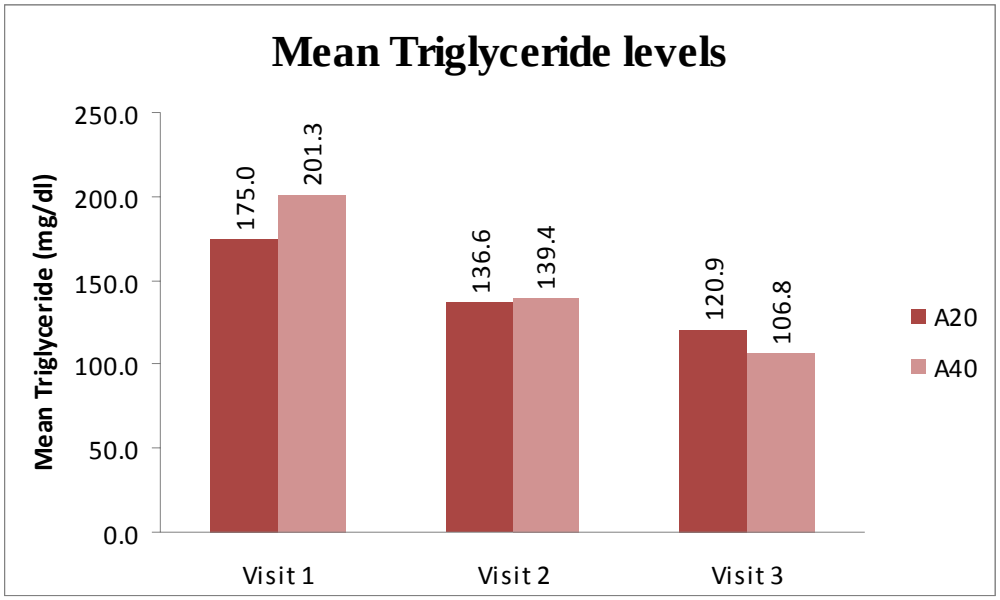
10. Comparison of Triglycerides between A20 and A40

Table No: 16 Triglycerides

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	Mean	174.97	136.63	120.87
	Std. Deviation	29.188	22.474	19.722
A40 (Atorvastatin 40)	Mean	201.33	139.43	106.77
	Std. Deviation	32.436	34.345	21.580
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of triglycerides was found to be statistically significant and the graphical representation is shown in Fig No: 11

Fig No: 11



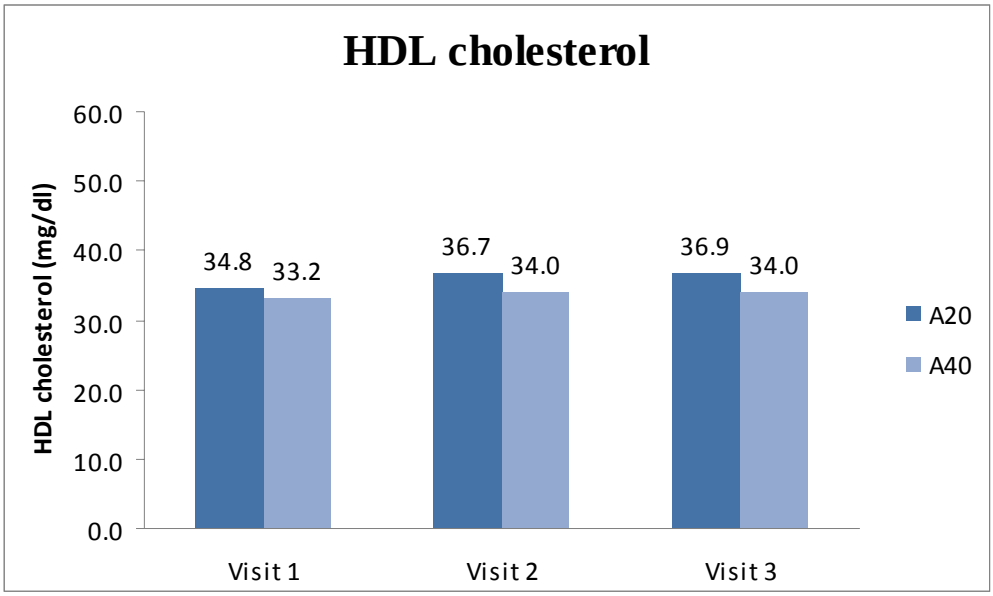
11. Comparison of HDL between A20 and A40

Table No: 17 HDL

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	Mean	34.80	36.73	36.93
	Std. Deviation	3.326	3.028	3.016
A40 (Atorvastatin 40)	Mean	33.17	34.03	34.03
	Std. Deviation	3.573	3.605	5.875
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of HDL with two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 12

Fig No: 12



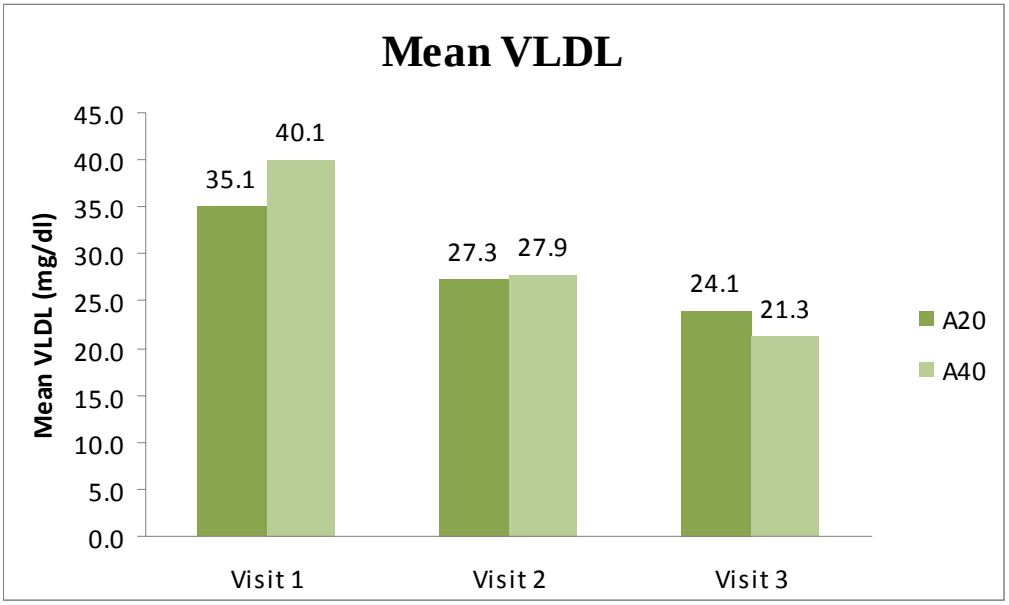
12. Comparison of VLDL between A20 and A40

Table No: 18 VLDL

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	**Mean**	**35.13**	**27.27**	**24.07**
	Std. Deviation	**6.191**	**4.608**	**3.982**
A40 (Atorvastatin 40)	**Mean**	**40.10**	**27.87**	**21.27**
	Std. Deviation	**6.424**	**6.827**	**4.266**
p value		**<0.05**		

When chi square test was done, p value was <0.05. So, the comparison of VLDL with the two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 13

Fig No: 13



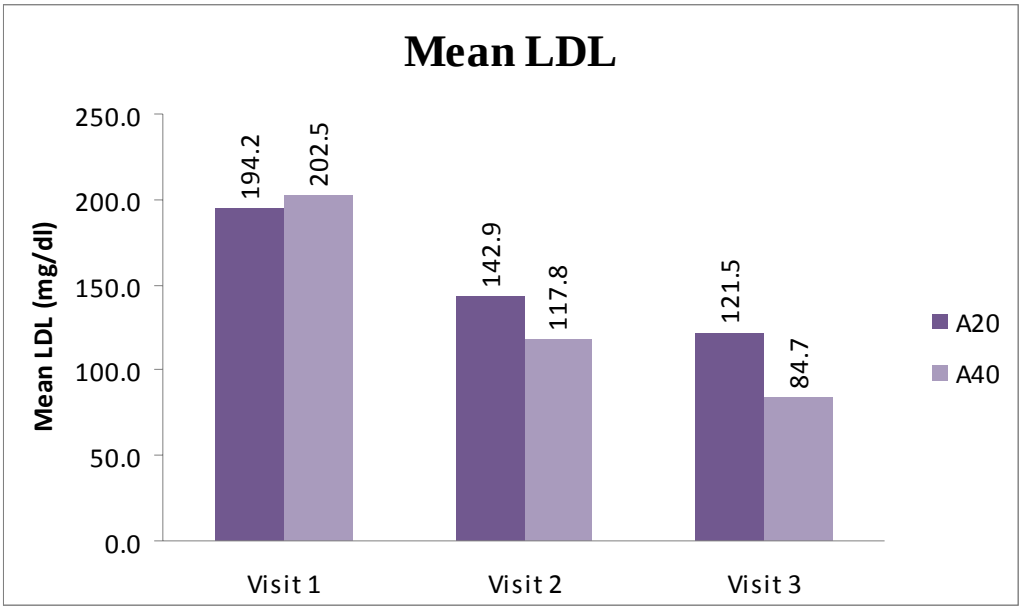
13. Comparison of LDL between A20 and A40

Table No: 19 LDL

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	**Mean**	**194.17**	**142.90**	**121.50**
	Std. Deviation	**30.744**	**28.521**	**22.218**
A40 (Atorvastatin 40)	**Mean**	**202.47**	**117.83**	**84.67**
	Std. Deviation	**27.645**	**32.748**	**19.759**
p value		**<0.05**		

When chi square test was done, p value was <0.05. So, the comparison of LDL with the two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 14

Fig No: 14



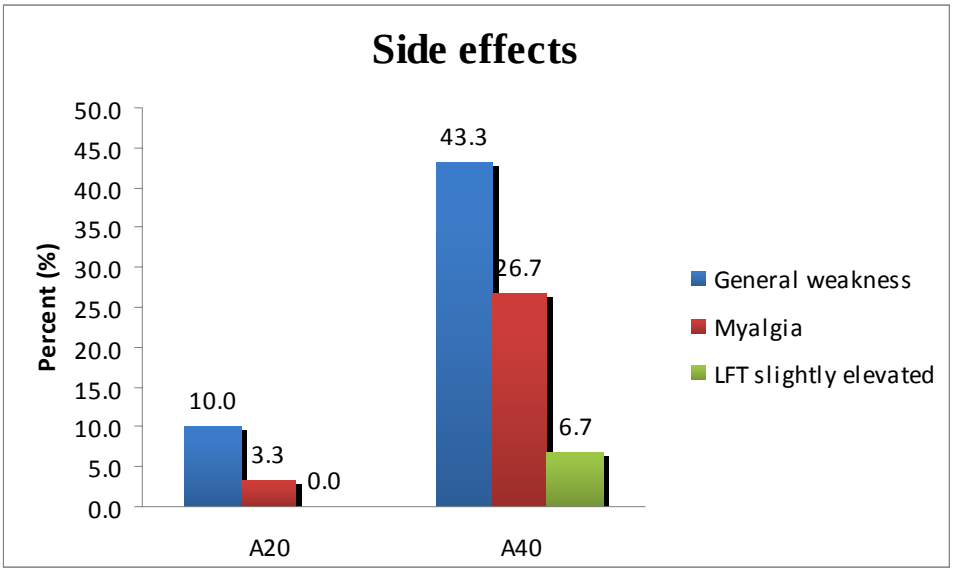
14. Comparison of Side effects between A20 and A40

Table No: 20 Side effects

Side effects		Drug	
		A20 (Atorvastatin 20)	A40 (Atorvastatin 40)
General Weakness	No: of patients	3	13
	Percentage of patients	10.0%	43.3%
Myalgia	No: of patients	1	8
	Percentage of patients	3.3%	26.7%
LFT slightly elevated	No: of patients	0	2
	Percentage of patients	0	6.7%

Statistical analysis using Pearson Chi-Square test shows that p value was <0.05. Hence statistically it is significant and the graphical representation is shown in Fig No: 15

Fig No: 15



COMPARISON OF A20 WITH S40

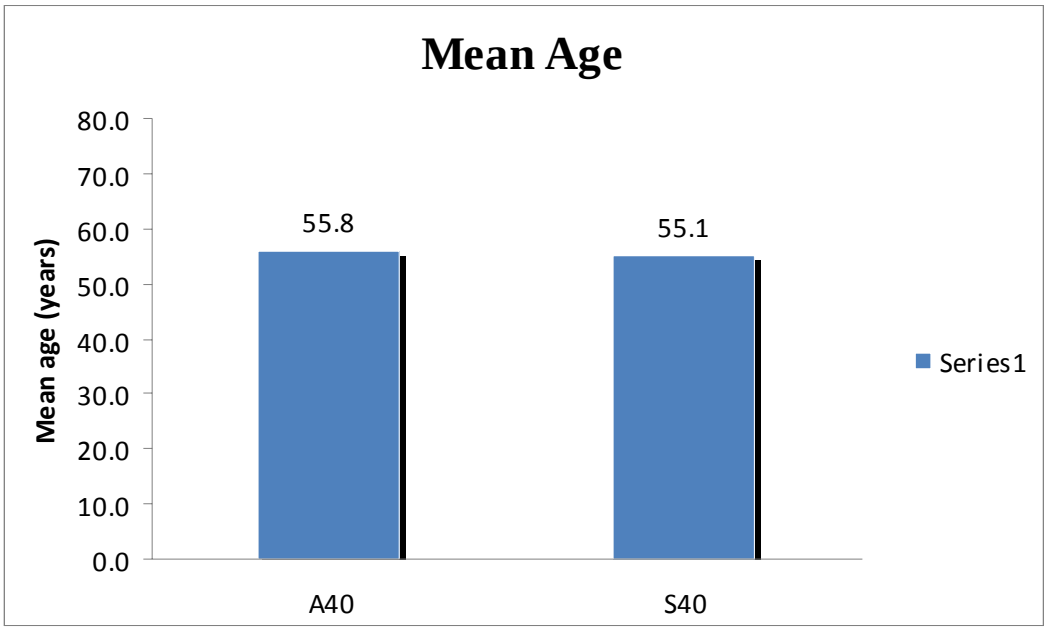
1. Comparison of Age between A20 and S40

Table No: 21 Age Distribution

Drug	Mean	Std. Deviation	p value
A20 (Atorvastatin 20)	**55.03**	**10.220**	**0.980**
S40 (Simvastatin40)	**55.10**	**10.287**	

When chi square test was done, p value was 0.980. So, there was no statistically significant difference between age distribution and the two study groups and the graphical representation is shown in Fig No: 16

Fig No: 16



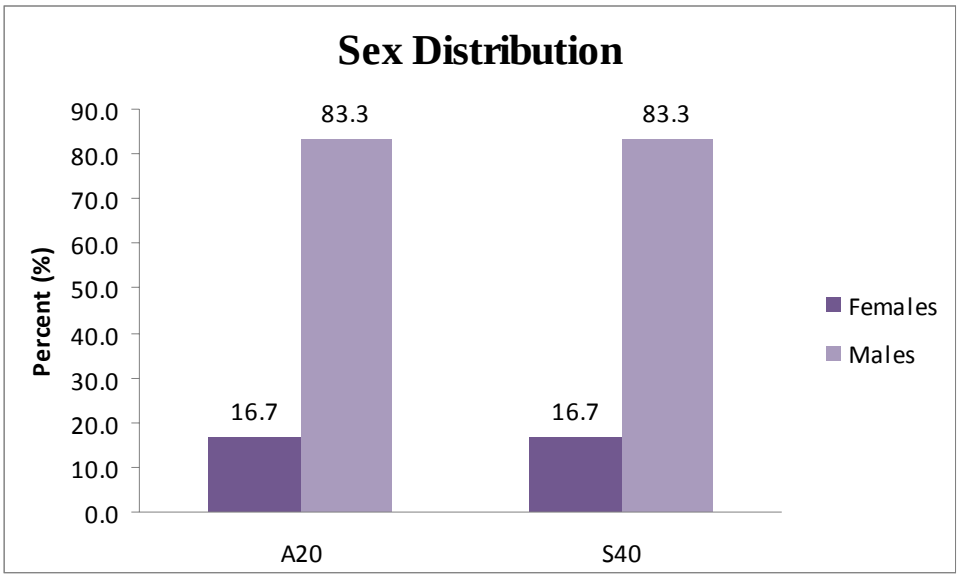
2. Comparison of Sex Distribution between A20 and S40

Table No: 22 Sex Distribution

Sex Distribution		Drug		p value
		A20 (Atorvastatin 20)	S40 (Simvastatin 40)	
Female	No: of patients	5	5	1.000
	Percentage of patients	16.7%	16.7%	
Male	No: of patients	25	25	
	Percentage of patients	83.3%	83.3%	

When Pearson Chi-Square test was done, p value was 1.000. So, there was no statistically significant difference between Sex Distribution and the two study groups and the graphical representation is shown in Fig No: 17

Fig No: 17



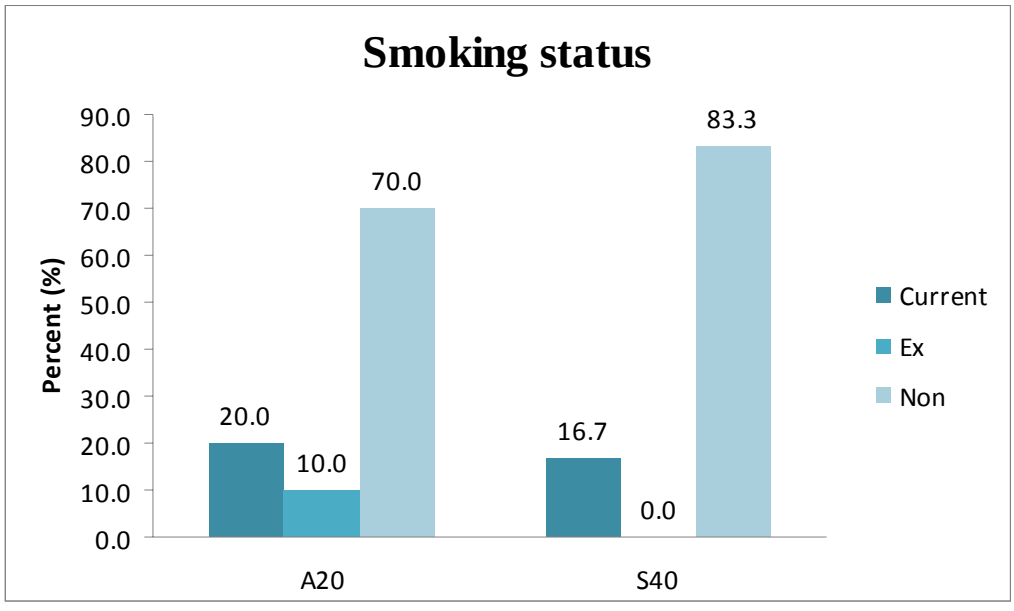
3. Comparison of Smoking between A20 and S40

Table No: 23 Smoking status

Smoking		Drug	
		A20 (Atorvastatin 20)	S40 (Simvastatin 40)
Current-Smoker	No: of patients	6	5
	Percentage of patients	20.0%	16.7%
Ex-Smoker	No: of patients	3	0
	Percentage of patients	10.0%	.0%
Non Smoker	No: of patients	21	25
	Percentage of patients	70.0%	83.3%

Statistical analysis using Fisher's Exact Test shows that p value is 1.000. Hence statistically it is not significant and the graphical representation is shown in Fig No: 18

Fig No: 18



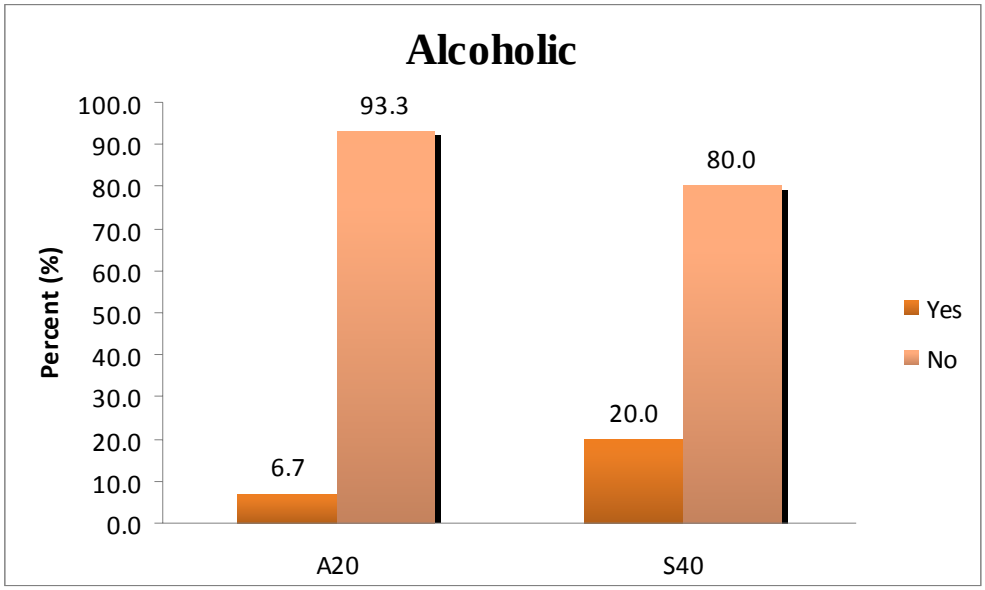
4. Comparison of Alcoholics between A20 and S40

Table No: 24 Alcoholics

Alcoholic		Drug	
		A20 (Atorvastatin 20)	**S40 (Simvastatin 40)**
Present	**No: of patients**	**2**	**6**
	Percentage of patients	**6.7%**	**20.0%**
Absent	**No: of patients**	**28**	**24**
	Percentage of patients	**93.3%**	**80.0%**

Statistical analysis using Fisher's Exact Test shows that p value is 0.254. Hence statistically it is not significant and the graphical representation is shown in Fig No: 19

Fig No: 19



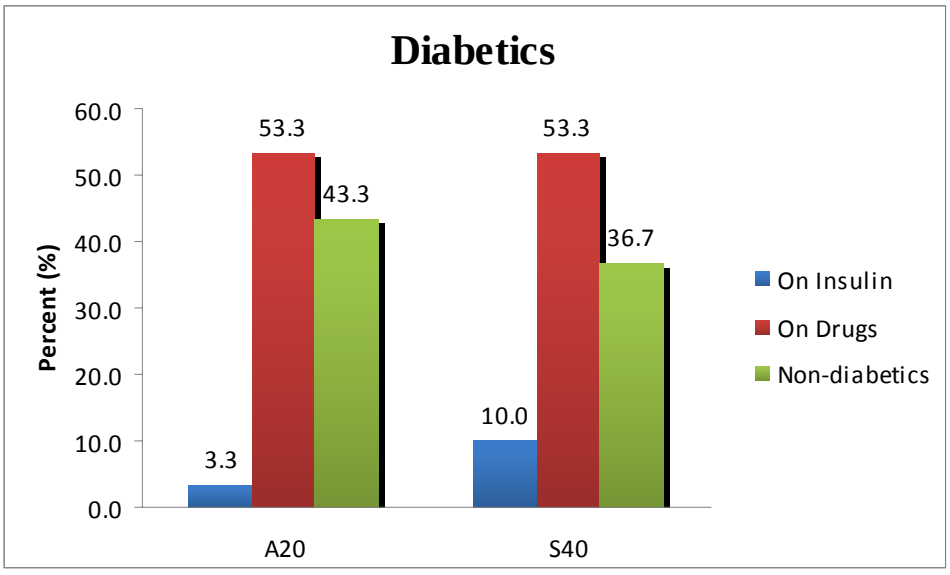
5. Comparison of Diabetes between A20 and S40

Table No: 25 Diabetes

Diabetics		Drug	
		A20 (Atorvastatin 20)	S40 (Simvastatin 40)
On Insulin	No: of patients	1	3
	Percentage of patients	3.3%	10.0%
On Drugs	No: of patients	16	16
	Percentage of patients	53.3%	53.3%
Non Diabetic	No: of patients	13	11
	Percentage of patients	43.4%	36.7%

Statistical analysis using Pearson Chi-Square shows that p value is 1.000. Hence statistically it is not significant and the graphical representation is shown in Fig No: 20

Fig No: 20



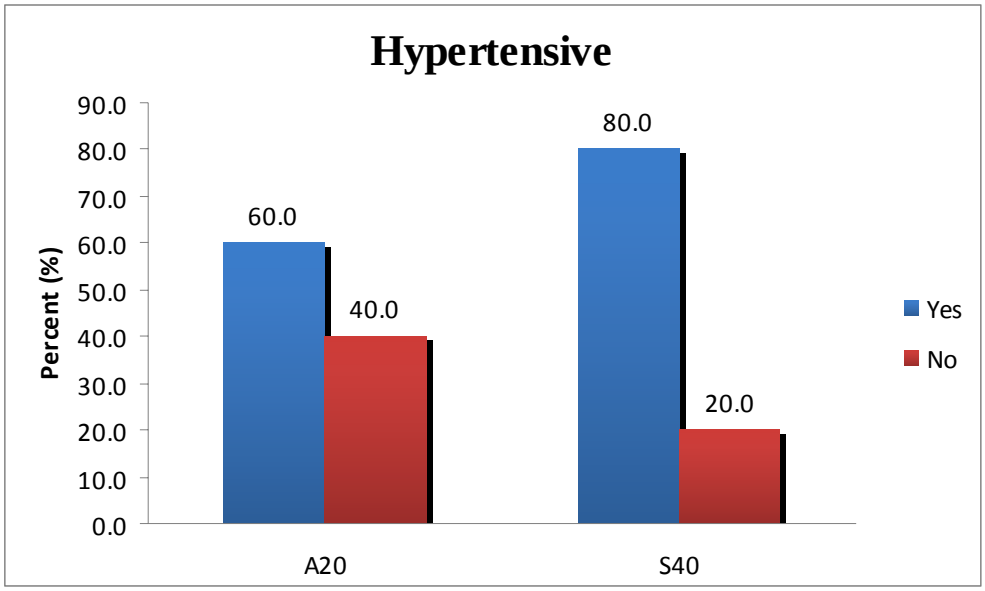
6. Comparison of Hypertension between A20 and S40

Table No: 26 Hypertension

Hypertension		Drug	
		A20 (Atorvastatin 20)	S40 (Simvastatin 40)
Hypertensive	No: of patients	18	24
	Percentage of patients	60.0%	80.0%
Normotensive	No: of patients	12	6
	Percentage of patients	40.0%	20.0%

Statistical analysis using Pearson Chi-Square shows that p value is 0.091. Hence statistically it is not significant and the graphical representation is shown in Fig No: 21

Fig No: 21



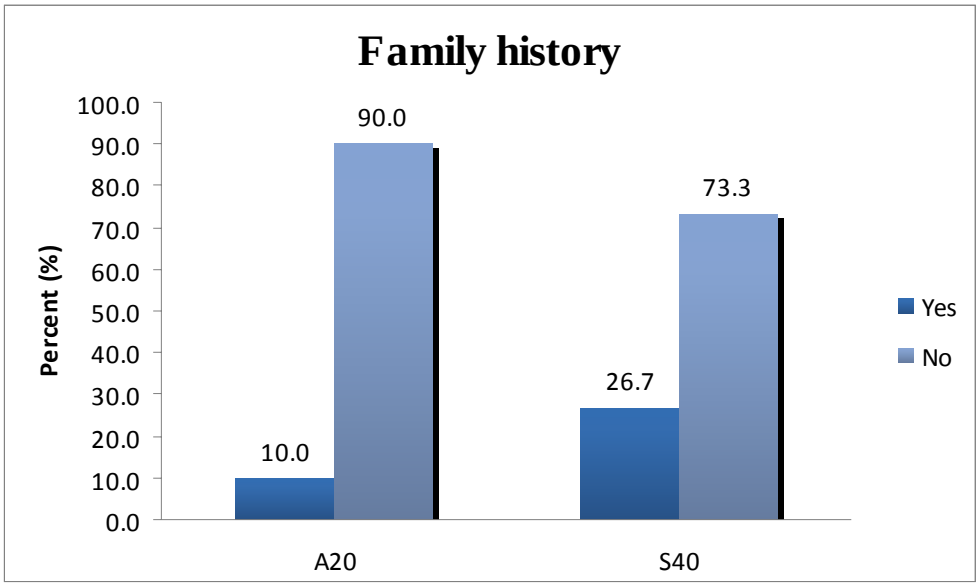
7. Comparison of Family History between A20 and S40

Table No: 27 Family History

Family History		Drug	
		A20 (Atorvastatin 20)	**S40 (Simvastatin 40)**
Present	**No: of patients**	**3**	**8**
	Percentage of patients	**10.0%**	**26.7%**
Absent	**No: of patients**	**27**	**22**
	Percentage of patients	**90.0%**	**73.3%**

Statistical analysis using Fisher's Exact Test shows that p value is 0.095. Hence statistically it is not significant and the graphical representation is shown in Fig No: 22

Fig No: 22



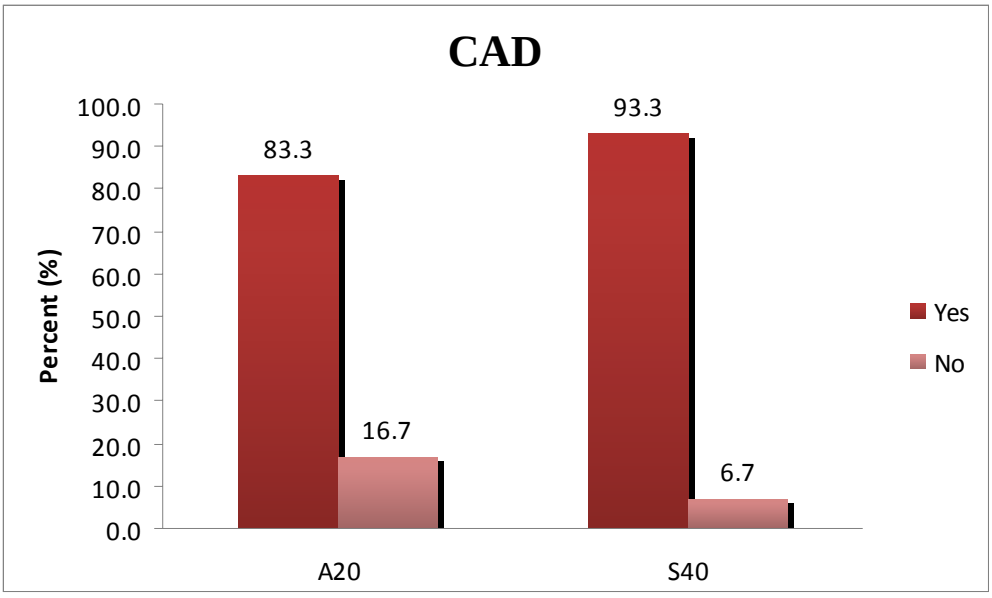
8. Comparison of Cardiovascular events between A20 and S40

Table No: 28 Cardiovascular events

CAD		Drug	
		A20 (Atorvastatin 20)	S40 (Simvastatin 40)
Present	No: of patients	25	28
	Percentage of patients	83.3%	93.3%
Absent	No: of patients	5	2
	Percentage of patients	16.7%	6.7%

Statistical analysis using Fisher's Exact Test shows that p value is 0.424. Hence statistically it is not significant and the graphical representation is shown in Fig No: 23

Fig No: 23



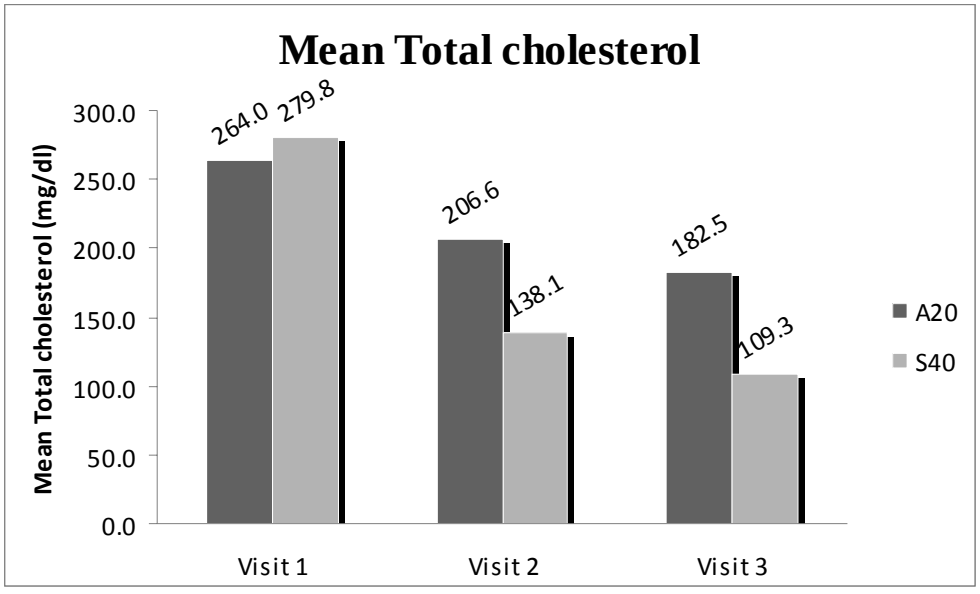
9. Comparison of Total Cholesterol between A20 and S40

Table No: 29 Total Cholesterol

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	Mean	264.00	206.57	182.47
	Std. Deviation	31.414	29.600	22.332
S40 (Simvastatin40)	Mean	279.80	138.10	109.27
	Std. Deviation	23.209	26.747	14.215
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of total cholesterol was found to be statistically significant and the graphical representation is shown in Fig No: 24

Fig No: 24



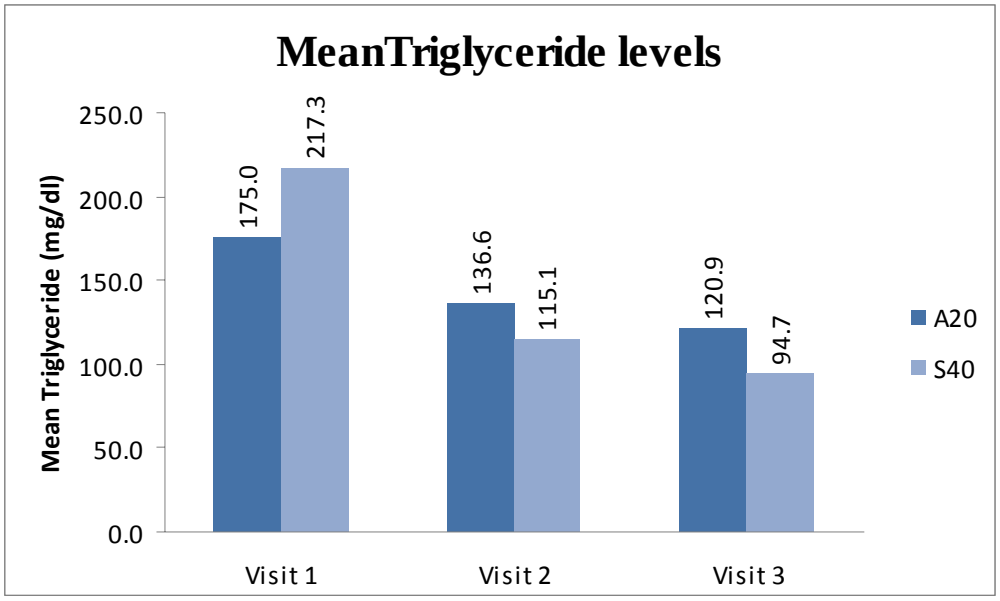
10. Comparison of Triglycerides between A20 and S40

Table No: 30 Triglycerides

Drug		Visit 1	Visit 2	Visit 3	p value
A20 (Atorvastatin 20)	Mean	174.97	136.63	120.87	<0.05
	Std. Deviation	29.188	22.474	19.722	
S40 (Simvastatin40)	Mean	217.33	115.07	94.73	
	Std. Deviation	41.501	25.557	16.148	

When chi square test was done, p value was <0.05. So, the comparison of triglycerides was found to be statistically significant and the graphical representation is shown in Fig No: 25

Fig No: 25



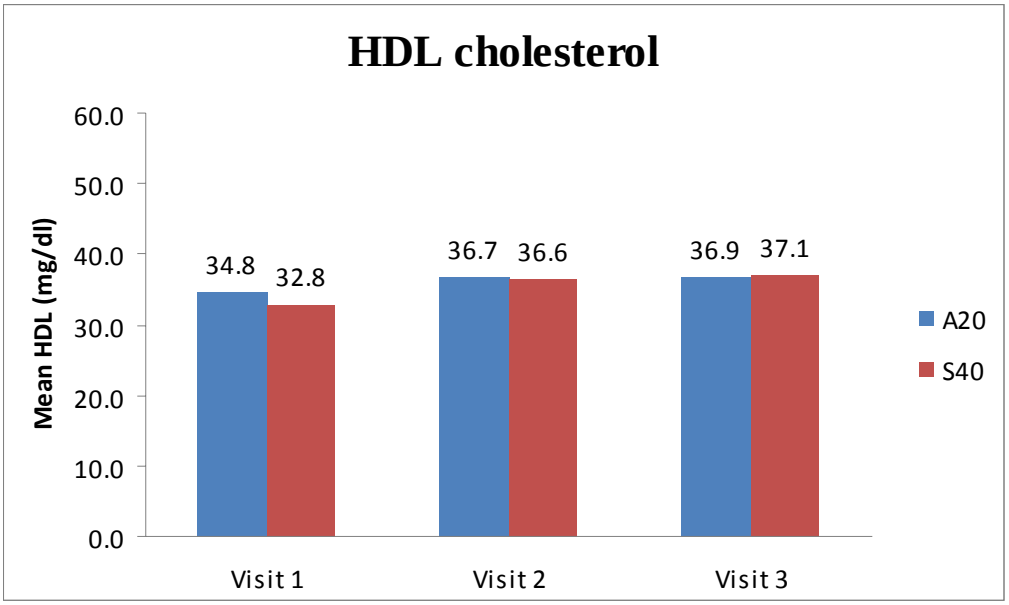
11. Comparison of HDL between A20 and S40

Table No: 31 HDL

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	Mean	34.80	36.73	36.93
	Std. Deviation	3.326	3.028	3.016
S40 (Simvastatin40)	Mean	32.83	36.63	37.10
	Std. Deviation	3.384	4.238	3.845
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of HDL with two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 26

Fig No: 26



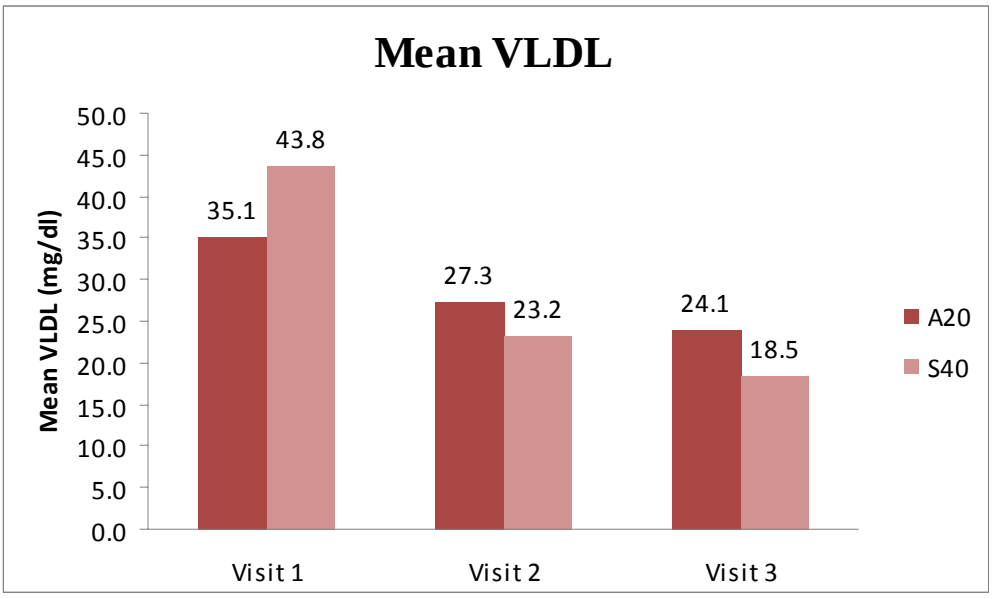
12. Comparison of VLDL between A20 and S40

Table No: 32 VLDL

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	Mean	35.13	27.27	24.07
	Std. Deviation	6.191	4.608	3.982
S40 (Simvastatin40)	Mean	43.77	23.20	18.47
	Std. Deviation	9.265	5.235	3.350
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of VLDL with the two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 27

Fig No: 27



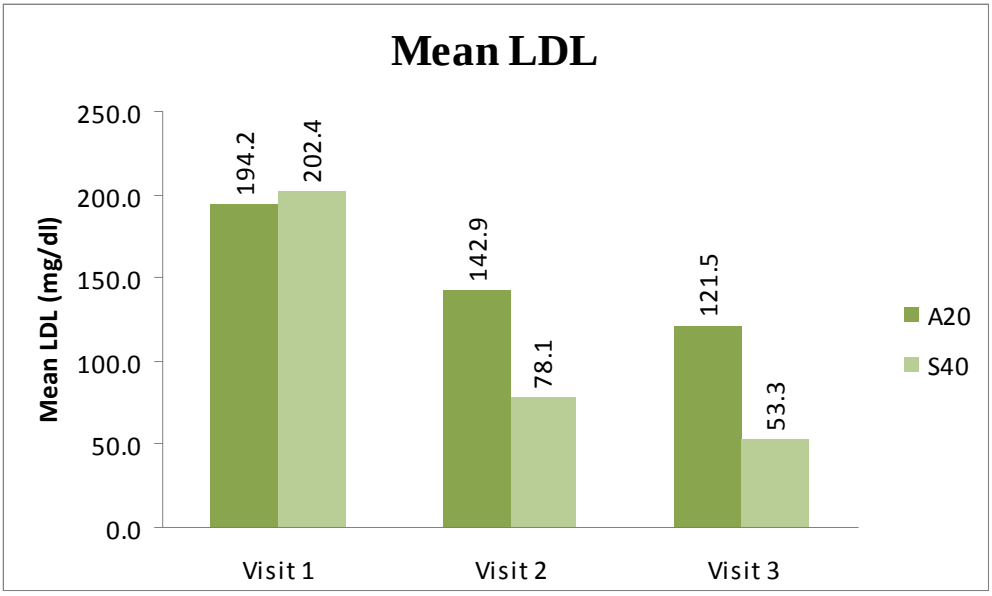
13. Comparison of LDL between A20 and S40

Table No: 33 LDL

Drug		Visit 1	Visit 2	Visit 3
A20 (Atorvastatin 20)	Mean	194.17	142.90	121.50
	Std. Deviation	30.744	28.521	22.218
S40 (Simvastatin40)	Mean	202.43	78.10	53.30
	Std. Deviation	24.060	24.493	12.123
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of LDL with the two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 28

Fig No: 28



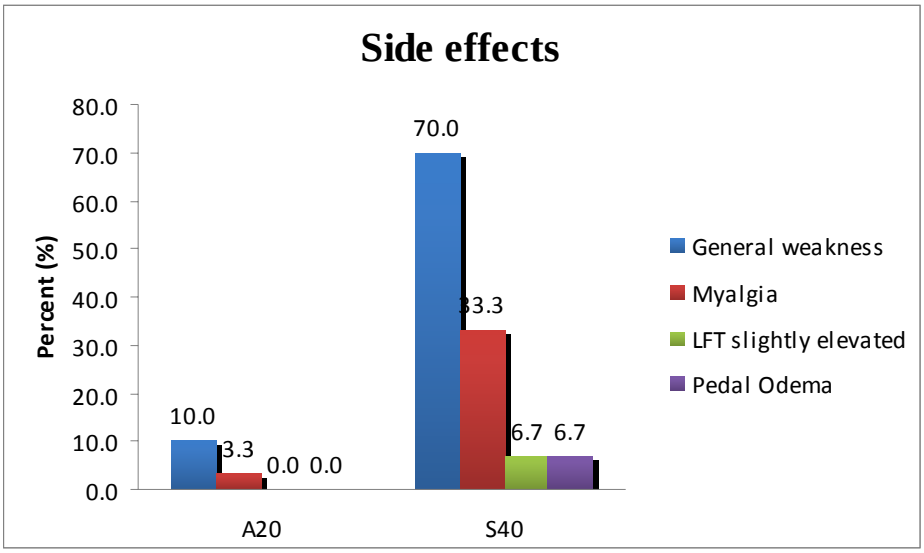
14. Comparison of Side effects between A20 and S40

Table No: 34 Side effects

Side effects		Drug	
		A20 (Atorvastatin 20)	S40 (Simvastatin 40)
General Weakness	No: of patients	3	21
	Percentage of patients	10.0%	70.0%
Myalgia	No: of patients	1	10
	Percentage of patients	3.3%	33.3%
LFT slightly elevated	No: of patients	0	2
	Percentage of patients	0	6.7%
Pedal Odema	No: of patients	0	2
	Percentage of patients	0	6.7%

Statistical analysis using Pearson Chi-Square test shows that p value is <0.05. Hence statistically it is significant and the graphical representation is shown in Fig No: 29

Fig No: 29



COMPARISON OF A40 WITH S40

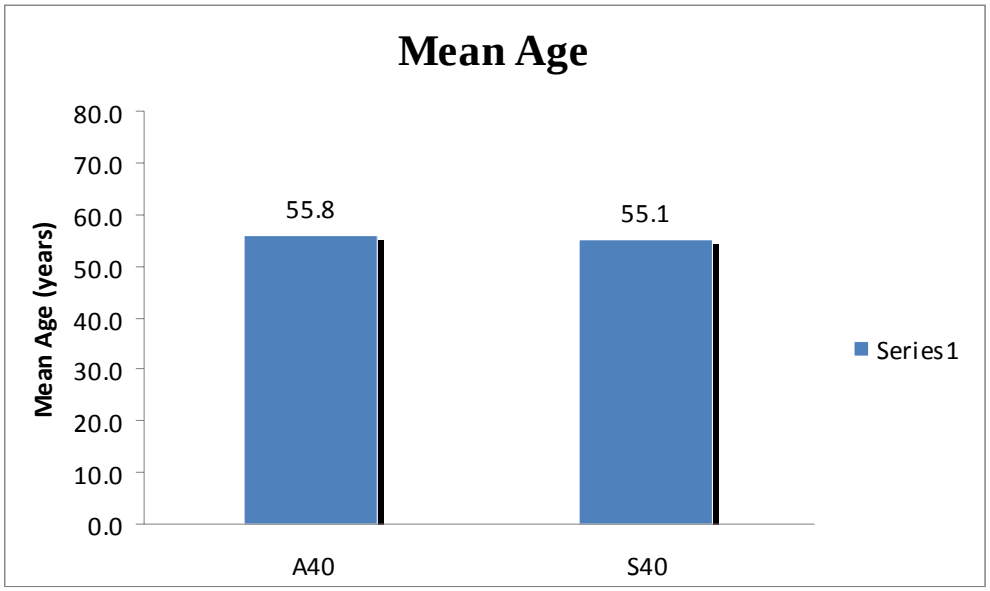
1. Comparison of Age Distribution between A40 and S40

Table No: 35 Age Distribution

Drug	Mean	Std. Deviation	p value
A40 (Atorvastatin 40)	**55.83**	**10.751**	**0.788**
S40 (Simvastatin 40)	**55.10**	**10.287**	

When chi square test was done, p value was 0.788. So, there was no statistically significant difference between age distribution and the two study groups and the graphical representation is shown in Fig No: 30

Fig No: 30



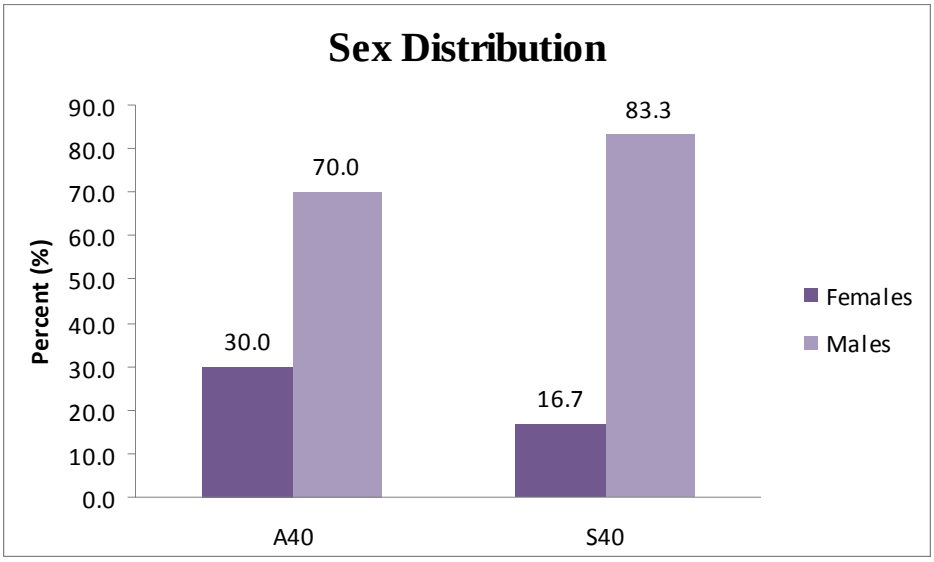
2. Comparison of Sex Distribution between A40 and S40

Table No: 36 Sex Distribution

Sex		Drug		p value
		A40 (Atorvastatin 40)	S40 (Simvastatin 40)	
Female	No: of patients	9	5	0.222
	Percentage of patients	30.0%	16.7%	
Male	No: of patients	21	25	
	Percentage of patients	70.0%	83.3%	

When Pearson Chi-Square test was done, p value was 0.222. So, there was no statistically significant difference between Sex Distribution and the two study groups and the graphical representation is shown in Fig No: 31

Fig No: 31



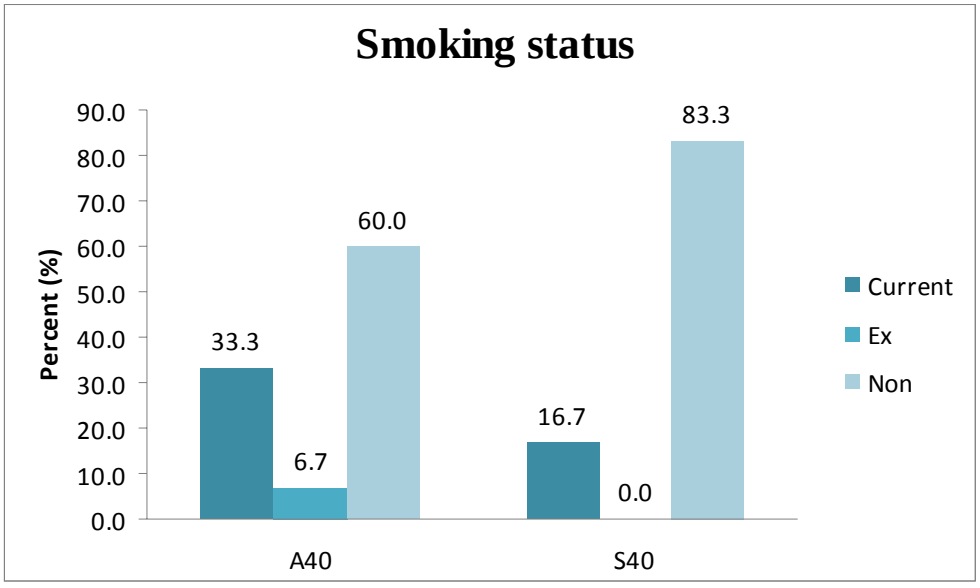
3. Comparison of Smoking between A40 and S40

Table No: 37 Smoking Status

Smoking		Drug	
		A40 (Atorvastatin 40)	S40 (Simvastatin 40)
Current-Smoker	No: of patients	10	5
	Percentage of patients	33.3%	16.7%
Ex-Smoker	No: of patients	2	0
	Percentage of patients	6.7%	.0%
Non Smoker	No: of patients	18	25
	Percentage of patients	60.0%	83.3%

Statistical analysis using Fisher's Exact Test shows that p value is 0.492. Hence statistically it is not significant and the graphical representation is shown in Fig No: 32

Fig No: 32



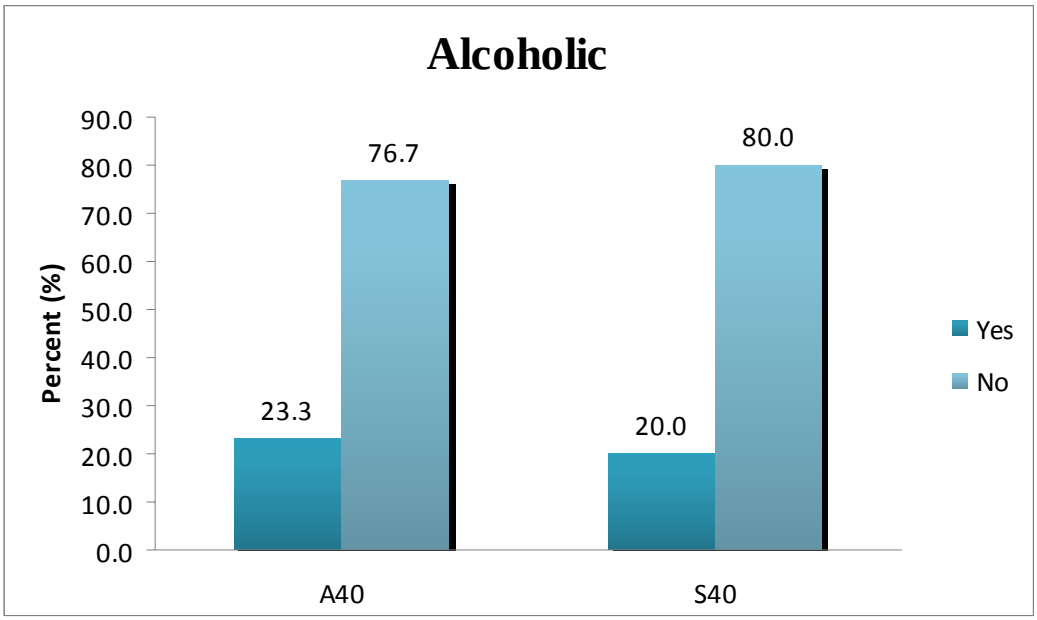
4. Comparison of Alcoholics between A40 and S40

Table No: 38 Alcoholics

Alcoholic		Drug	
		A40 (Atorvastatin 40)	**S40 (Simvastatin 40)**
Present	**No: of patients**	**7**	**6**
	Percentage of patients	**23.3%**	**20.0%**
Absent	**No: of patients**	**23**	**24**
	Percentage of patients	**76.7%**	**80.0%**

Statistical analysis using Pearson Chi-Square shows that p value is 0.754. Hence statistically it is not significant and the graphical representation is shown in Fig No: 33.

Fig No: 33



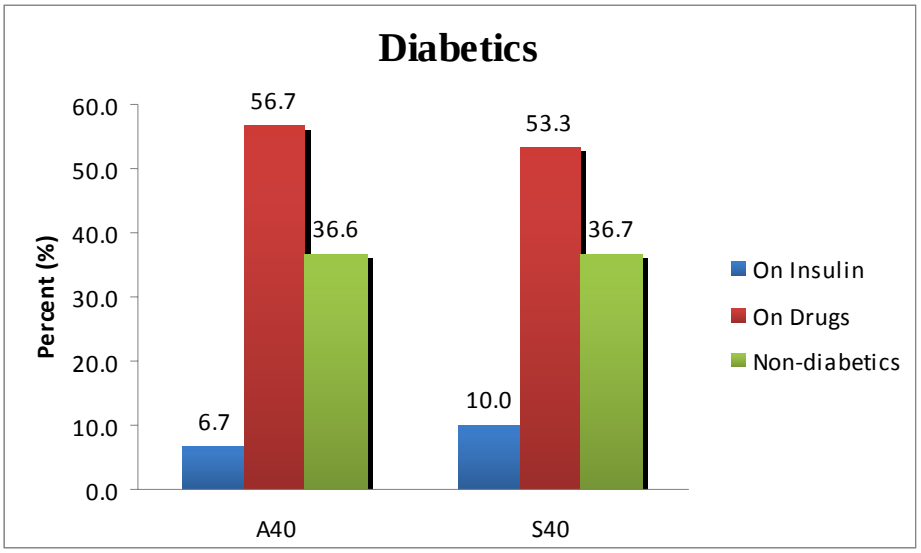
5. Comparison of Diabetes between A40 and S40

Table No: 39 Diabetes

Diabetics		Drug	
		A40 (Atorvastatin 40)	S40 (Simvastatin 40)
On Insulin	No: of patients	2	3
	Percentage of patients	6.7%	10.0%
On Drugs	No: of patients	17	16
	Percentage of patients	56.7%	53.3%
Non Diabetic	No: of patients	11	11
	Percentage of patients	36.6%	36.7%

Statistical analysis using Pearson Chi-Square shows that p value is 0.795. Hence statistically it is not significant and the graphical representation is shown in Fig No: 34.

Fig No: 34



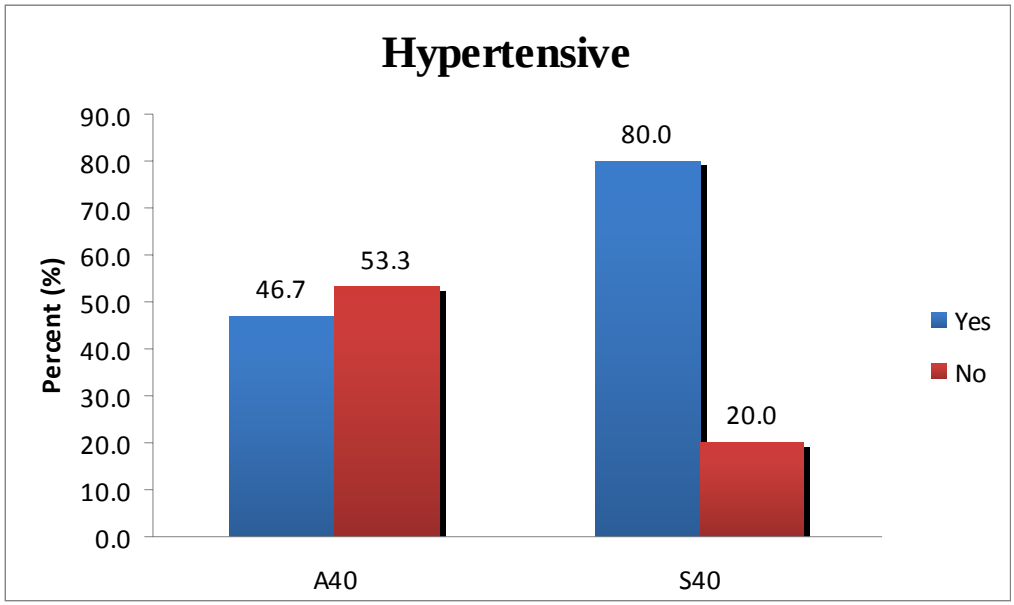
6. Comparison of Hypertension between A40 and S40

Table No: 40 Hypertension

Hypertension		Drug	
		A40 (Atorvastatin 40)	S40 (Simvastatin 40)
Hypertensive	No: of patients	14	24
	Percentage of patients	46.7%	80.0%
Normotensive	No: of patients	16	6
	Percentage of patients	53.3%	20.0%

Statistical analysis using Pearson Chi-Square shows that p value is 0.007. Hence statistically it is significant and the graphical representation is shown in Fig No: 35.

Fig No: 35



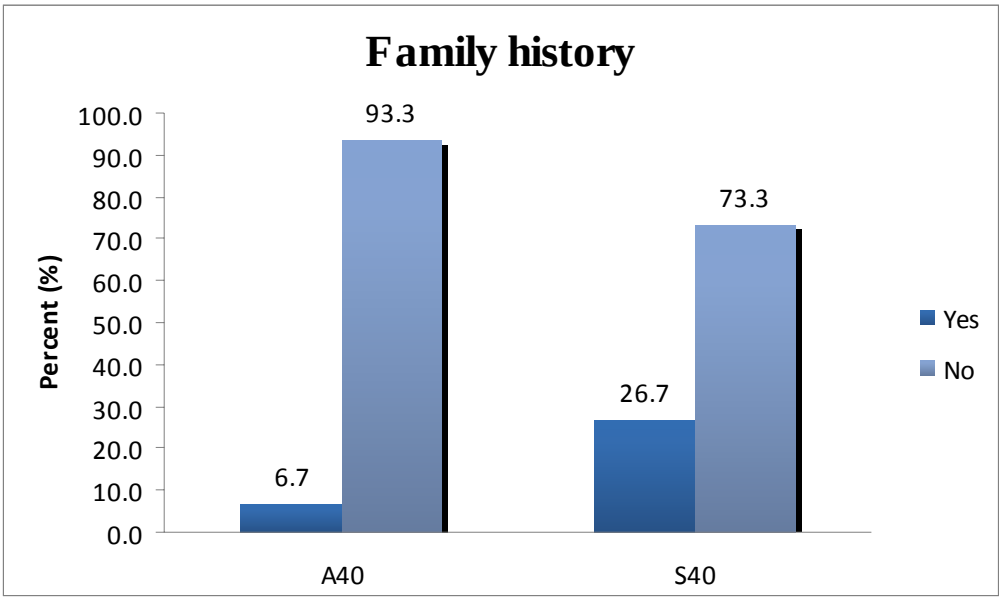
7. Comparison of Family History between A40 and S40

Table No: 41 Family History

Family History		Drug	
		A40 (Atorvastatin 40)	S40 (Simvastatin 40)
Present	No: of patients	2	8
	Percentage of patients	6.7%	26.7%
Absent	No: of patients	28	22
	Percentage of patients	93.3%	73.3%

Statistical analysis using Pearson Chi-Square shows that p value is 0.038. Hence statistically it is significant and the graphical representation is shown in Fig No: 36.

Fig No: 36



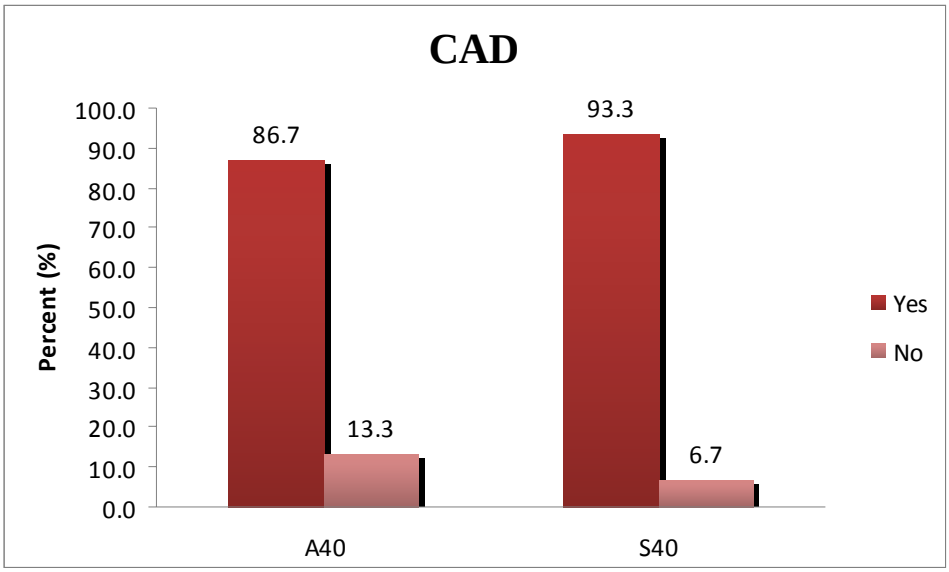
8. Comparison of Cardiovascular events between A40 and S40

Table No: 42 Cardiovascular events

CAD		Drug	
		A40 (Atorvastatin 40)	**S40 (Simvastatin 40)**
Present	**No: of patients**	**26**	**28**
	Percentage of patients	**86.7%**	**93.3%**
Absent	**No: of patients**	**4**	**2**
	Percentage of patients	**13.3%**	**6.7%**

Statistical analysis using Fisher's Exact Test shows that p value is 0.671. Hence statistically it is not significant and the graphical representation is shown in Fig No: 37

Fig No: 37



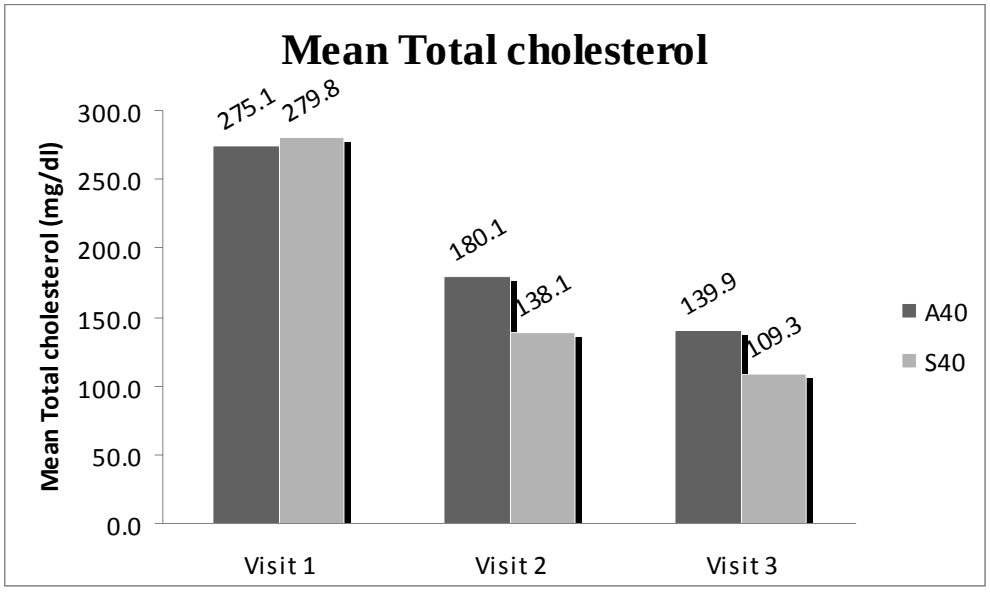
9. Comparison of Total Cholesterol between A40 and S40

Table No: 43 Total Cholesterol

Drug		Visit 1	Visit 2	Visit 3
A40 (Atorvastatin 40)	Mean	275.10	180.07	139.90
	Std. Deviation	27.353	30.674	19.090
S40 (Simvastatin 40)	Mean	279.80	138.10	109.27
	Std. Deviation	23.209	26.747	14.215
p value	<0.05			

When chi square test was done, p value was <0.05. So, the comparison of total cholesterol was found to be statistically significant and the graphical representation is shown in Fig No: 38.

Fig No: 38



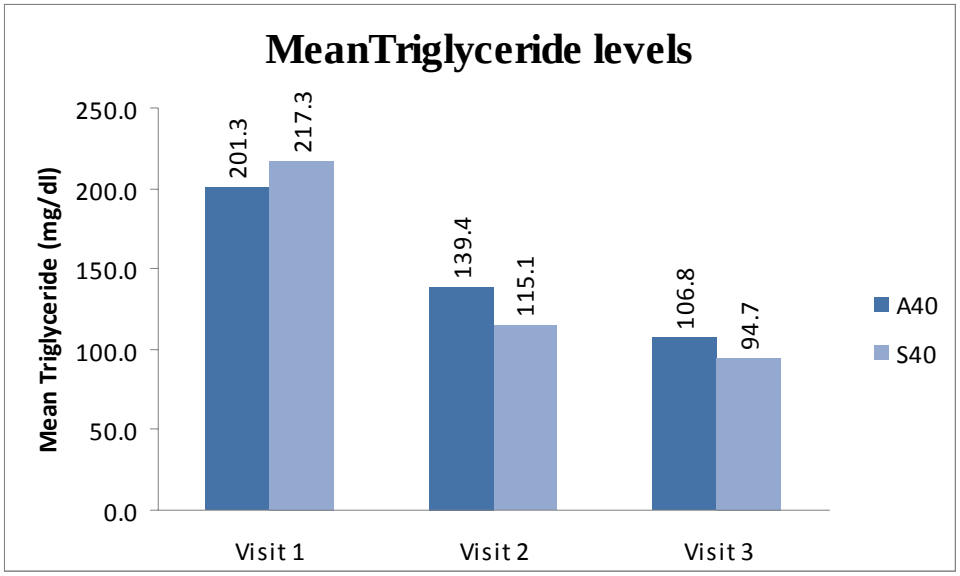
10. Comparison of Triglycerides between A40 and S40

Table No: 44 Triglycerides

Drug		Visit 1	Visit 2	Visit 3
A40 (Atorvastatin 40)	Mean	201.33	139.43	106.77
	Std. Deviation	32.436	34.345	21.580
S40 (Simvastatin 40)	Mean	217.33	115.07	94.73
	Std. Deviation	41.501	25.557	16.148
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of triglycerides was found to be statistically significant and the graphical representation is shown in Fig No: 39.

Fig No: 39



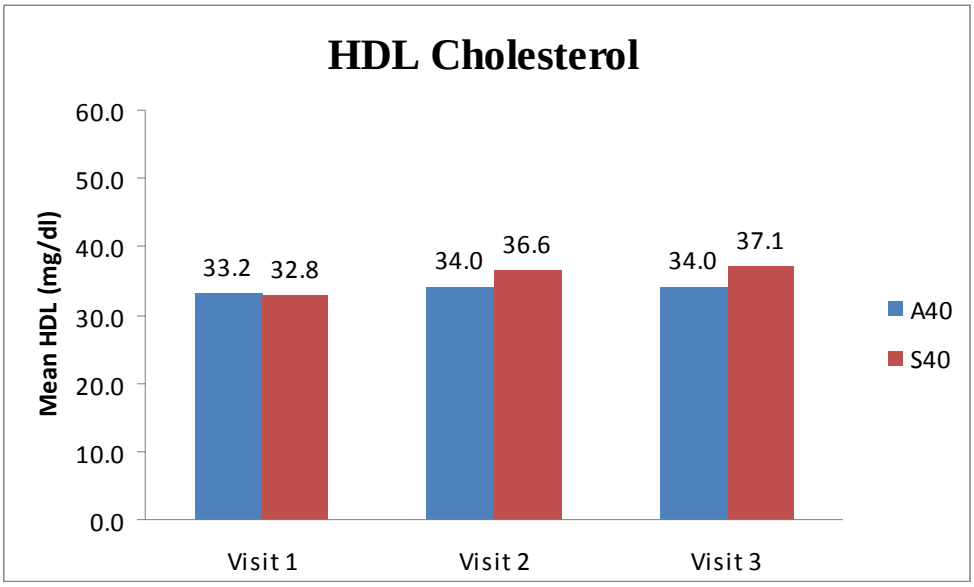
11. **Comparison of HDL between A40 and S40**

Table No: 45 HDL

Drug		Visit 1	Visit 2	Visit 3
A40 (Atorvastatin 40)	**Mean**	**33.17**	**34.03**	**34.03**
	Std. Deviation	**3.573**	**3.605**	**5.875**
S40 (Simvastatin 40)	**Mean**	**32.83**	**36.63**	**37.10**
	Std. Deviation	**3.384**	**4.238**	**3.845**
p value		**<0.05**		

When chi square test was done, p value was <0.05. So, the comparison of HDL with two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 40.

Fig No: 40



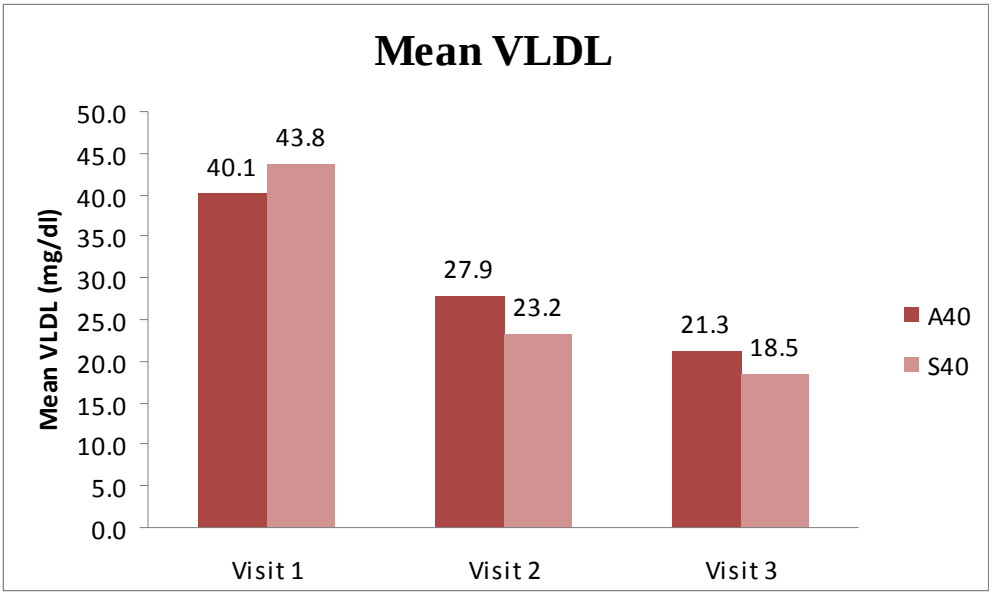
12. Comparison of VLDL between A40 and S40

Table No: 46 VLDL

Drug		Visit 1	Visit 2	Visit 3
A40 (Atorvastatin 40)	Mean	40.10	27.87	21.27
	Std. Deviation	6.424	6.827	4.266
S40 (Simvastatin 40)	Mean	43.77	23.20	18.47
	Std. Deviation	9.265	5.235	3.350
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of VLDL with the two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 41.

Fig No: 41



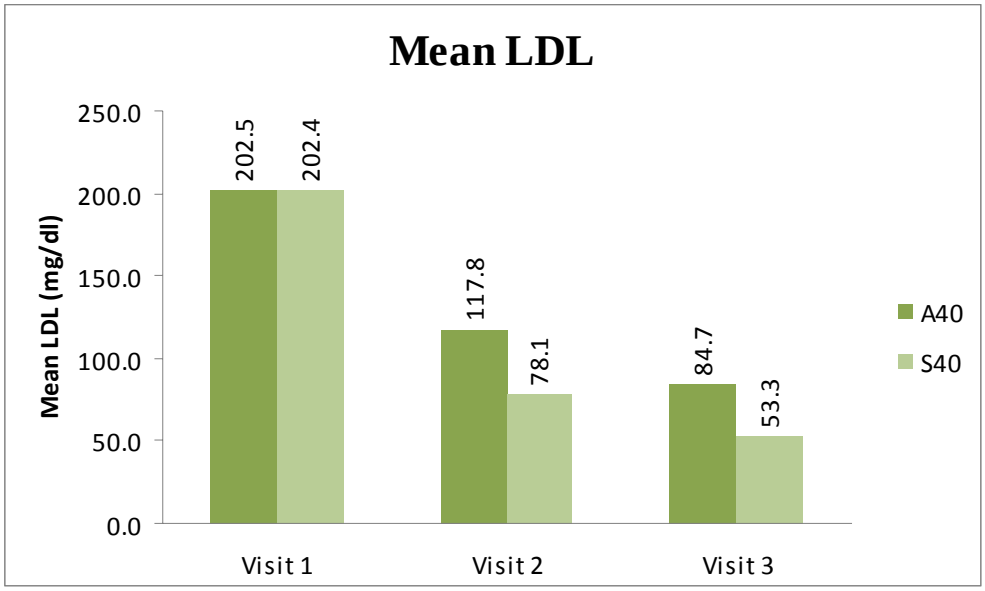
13. Comparison of LDL between A40 and S40

Table No: 47 LDL

Drug		Visit 1	Visit 2	Visit 3
A40 (Atorvastatin 40)	Mean	202.47	117.83	84.67
	Std. Deviation	27.645	32.748	19.759
S40 (Simvastatin 40)	Mean	202.43	78.10	53.30
	Std. Deviation	24.060	24.493	12.123
p value		<0.05		

When chi square test was done, p value was <0.05. So, the comparison of LDL with the two study groups was found to be statistically significant and the graphical representation is shown in Fig No: 42.

Fig No: 42



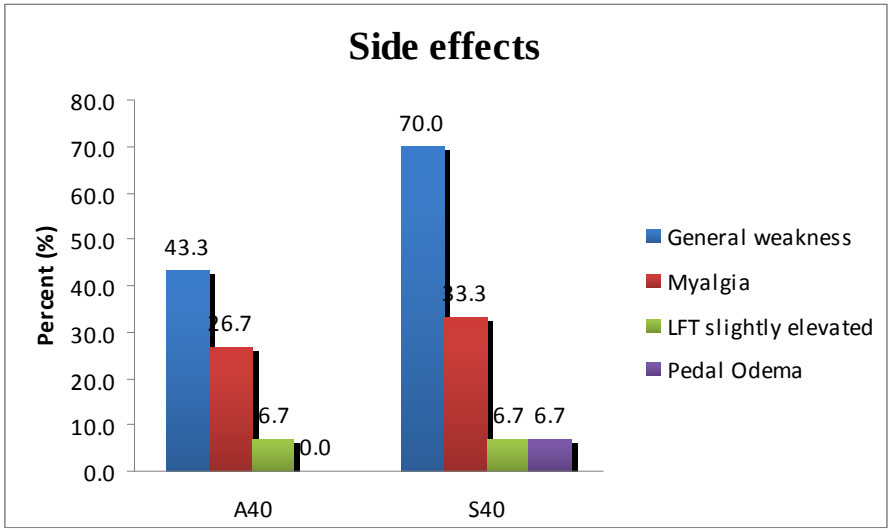
14. Comparison of Side effects between A40 and S40

Table No: 48 Side effects

Side effects		Drug	
		A40 (Atorvastatin 40)	S40 (Simvastatin 40)
General Weakness	No: of patients	13	21
	Percentage of patients	43.3%	70.0%
Myalgia	No: of patients	8	10
	Percentage of patients	26.7%	33.3%
LFT slightly elevated	No: of patients	2	2
	Percentage of patients	6.7%	6.7%
Pedal Odema	No: of patients	0	2
	Percentage of patients	0	6.7%

Statistical analysis using Pearson Chi-Square shows that p value is 0.037. Hence statistically it is significant and the graphical representation is shown in Fig No: 43.

Fig No: 43



COMPARATIVE EFFICACY

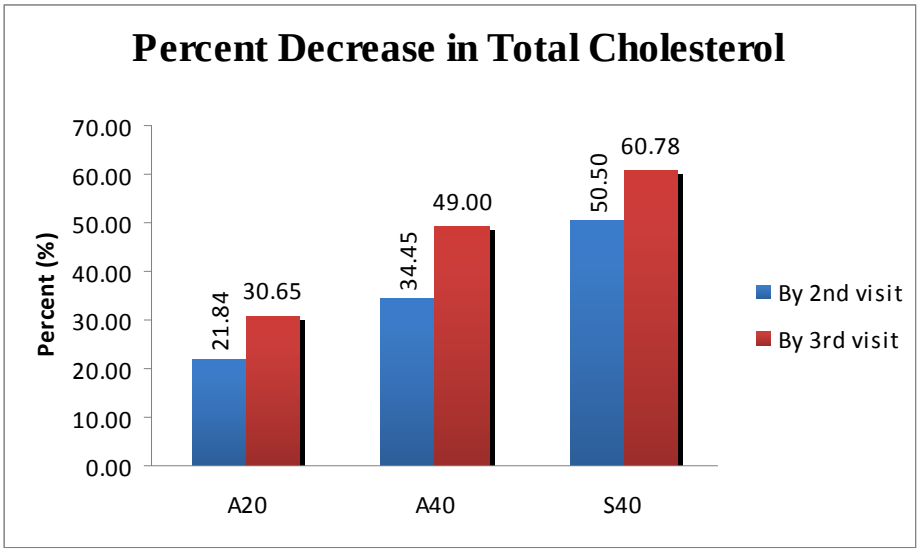
Percentage Changes in Total Cholesterol

Table No: 49 Percentage Changes in Total Cholesterol

Drug	Percentage Change TC12	Percentage Change TC13
A20 (Atorvastatin 20)	**21.8372**	**30.6483**
A40 (Atorvastatin 40)	**34.4525**	**49.0035**
S40 (Simvastatin 40)	**50.5037**	**60.7804**

The comparison of total cholesterol in Simvastatin and Atorvastatin patients were found to be statistically significant and the graphical representation is shown in Fig No: 44. It shows that Simvastatin 40 mg is better than Atorvastatin 40mg which is better than Atorvastatin 20mg in the reduction of total cholesterol.

Fig No: 44



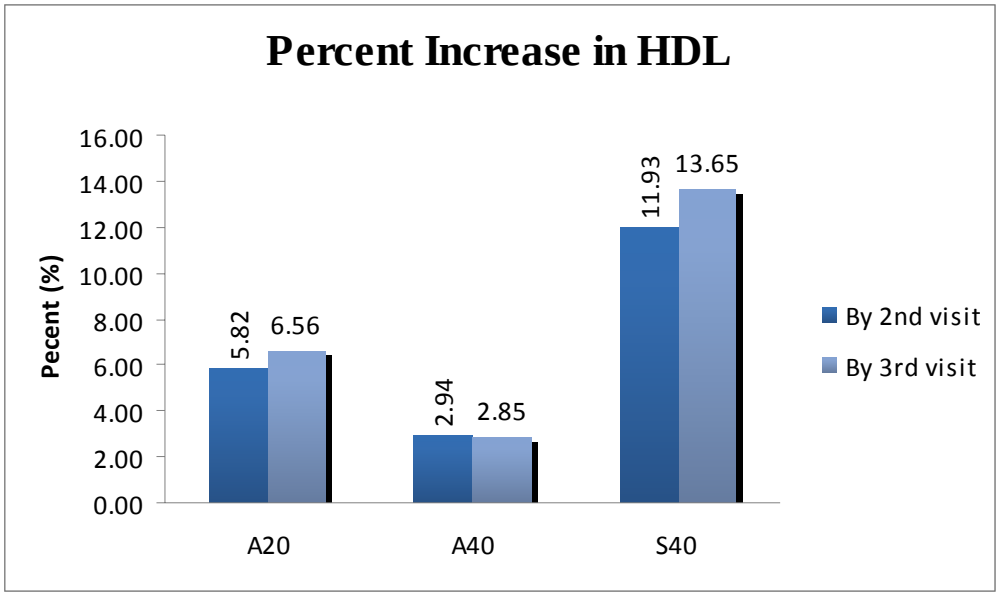
Percentage Changes in HDL

Table No: 50 Percentage Changes in HDL

Drug	Percentage Change HDL12	Percentage Change HDL13
A20 (Atorvastatin 20)	**5.8220**	**6.5578**
A40 (Atorvastatin 40)	**2.9446**	**2.8513**
S40 (Simvastatin 40)	**11.9324**	**13.6489**

The comparison of HDL in Simvastatin and Atorvastatin patients were found to be statistically significant and the graphical representation is shown in Fig No: 45. It shows that Simvastatin 40 mg is better than Atorvastatin 20mg which is better than Atorvastatin 40mg in the reduction of HDL.

Fig No: 45



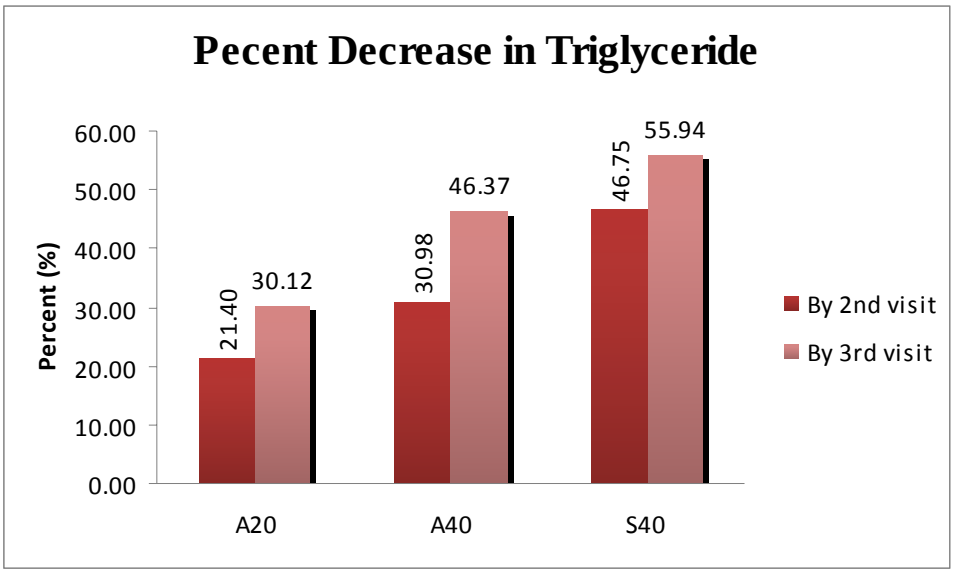
Percentage Changes in Triglycerides

Table No: 51 Percentage Changes in Triglycerides

Drug	Percentage Change TG12	Percentage Change TG13
A20 (Atorvastatin 20)	**21.3958**	**30.1197**
A40 (Atorvastatin 40)	**30.9766**	**46.3713**
S40 (Simvastatin 40)	**46.7485**	**55.9384**

The comparison of Triglycerides in Simvastatin and Atorvastatin patients were found to be statistically significant and the graphical representation is shown in Fig No: 46. It shows that Simvastatin 40 mg is better than Atorvastatin 40mg which is better than Atorvastatin 20mg in the reduction of Triglycerides.

Fig No: 46



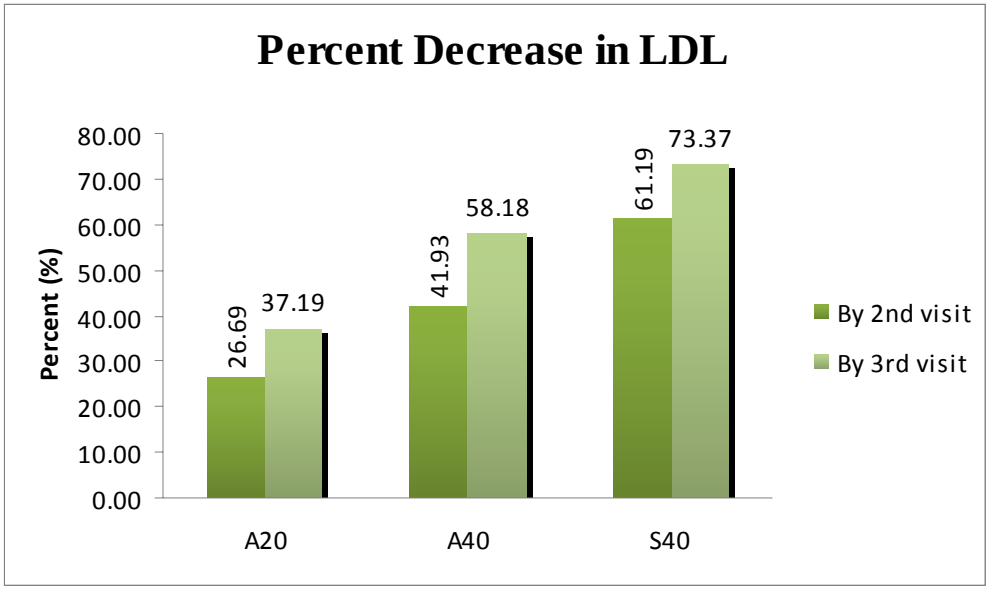
Percentage Changes in LDL

Table No: 52 Percentage Changes in LDL

Drug	Percentage Change LDL12	Percentage Change LDL13
A20 (Atorvastatin 20)	**26.6861**	**37.1870**
A40 (Atorvastatin 40)	**41.9303**	**58.1757**
S40 (Simvastatin 40)	**61.1929**	**73.3689**

The comparison of LDL in Simvastatin and Atorvastatin patients were found to be statistically significant and the graphical representation is shown in Fig No: 47. It shows that Simvastatin 40 mg is better than Atorvastatin 40mg which is better than Atorvastatin 20mg in the reduction of LDL.

Fig No: 47



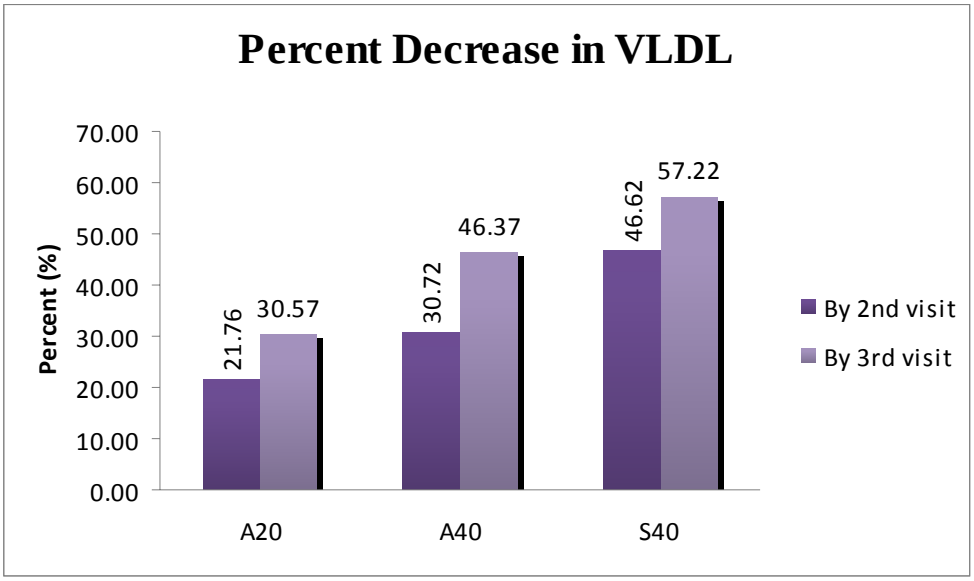
Percentage Changes in VLDL

Table No: 53 Percentage Changes in VLDL

Drug	Percentage Change VLDL12	Percentage Change VLDL13
A20 (Atorvastatin 20)	**21.7580**	**30.5711**
A40 (Atorvastatin 40)	**30.7205**	**46.3703**
S40 (Simvastatin 40)	**46.6156**	**57.2205**

The comparison of VLDL in Simvastatin and Atorvastatin patients were found to be statistically significant and the graphical representation is shown in Fig No: 48. It shows that Simvastatin 40 mg is better than Atorvastatin 40mg which is better than Atorvastatin 20mg in the reduction of VLDL.

Fig No: 48



DISCUSSION

The present study was designed to primarily compare efficacy and side effect profile of Simvastatin versus Atorvastatin at the doses prescribed in routine clinical practice. Due to the observational nature of this study, dose to dose comparisons between simvastatin and Atorvastatin relied mainly on the sample size available in each of the groups. Three comparisons are carried out in this study:

- Atorvastatin 20mg is compared with Atorvastatin 40mg.
- Atorvastatin 20mg is compared with Simvastatin 40mg.
- Atorvastatin 40mg is compared with Simvastatin 40mg.

This was a randomized controlled study, and there were some baseline differences between simvastatin and Atorvastatin treated patients. Patients were matched on relevant characteristics and co-morbidities before their data were abstracted.

The findings of the present study provide valuable information in aiding decisions on therapeutic drug selection for patients with Dyslipidemia in actual clinical practice settings. Furthermore, diet and exercise could also influence the results of patient's lipid levels.

Age Distribution and Dyslipidemia

The age differed in Atorvastatin 20, Atorvastatin 40 and Simvastatin 40 study groups as shown in Table No: 7, Table No: 21, Table No: 35. Thus there was no statistical significant difference between age and the study groups.

Sex Distribution and Dyslipidemia

The sex differed in Atorvastatin 20, Atorvastatin 40 and Simvastatin 40 study groups. Male patients were found to be higher when compared to female patients as shown in Table No: 8, Table No: 22, Table No: 36. Thus there was no statistical significant difference between sex and the study groups.

Smoking and Dyslipidemia

The smoking status differed in Atorvastatin 20, Atorvastatin 40 and Simvastatin 40 study groups as shown in Table No: 9, Table No: 23, Table No: 37. It shows that there was no statistical significant difference between smoking and the study groups.

Alcoholic and Dyslipidemia

The alcoholics differed in Atorvastatin 20, Atorvastatin 40 and Simvastatin 40 study groups as shown in Table No: 10, Table No: 24, Table No: 38. It shows that there was no statistical significant difference between alcoholism and the study groups.

Dyslipidemia and Diabetes Mellitus

Diabetes Mellitus is well a recognized risk factor for Dyslipidemia. In the present study, the diabetes alone was not an independent risk factor for the development of Dyslipidemia. There was no significant difference between diabetics and non diabetics.

Dyslipidemia and Hypertension

The comparison of dyslipidemia in Hypertensive patients did show any significant difference.

CAD and Dyslipidemia

The occurrence of CAD in patients who had taken Simvastatin 40mg is 93.3%, 86.7% in Atorvastatin 40mg and 83.3% in Atorvastatin 20mg.

Changes in Total Cholesterol

The present study was found that in second visit Atorvastatin 20mg reduces the total cholesterol by 21.84%, while Atorvastatin 40mg reduces the total cholesterol by 34.45%. In Third visit, Atorvastatin 20mg reduces the total cholesterol by 30.65% while Atorvastatin 40mg reduces the total cholesterol by 49%. Thus Atorvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 20mg reduces the total cholesterol by 21.84% while Simvastatin 40mg reduces the total cholesterol by 50.50%. In Third visit, Atorvastatin 20mg reduces the total cholesterol by 30.65% while Simvastatin 40mg reduces the total cholesterol by 60.78%. Thus Simvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 40mg reduces the total cholesterol by 34.45%, while Simvastatin 40mg reduces the total cholesterol by 50.50%. In Third visit, Atorvastatin 40mg reduces the total cholesterol by 49%, while Simvastatin 40mg reduces the total cholesterol by 60.78%. Thus Simvastatin 40mg is better than Atorvastatin 40mg.

Changes in High Density Lipoprotein levels

The present study was found that in second visit Atorvastatin 20mg increases the HDL by 5.82% while Atorvastatin 40mg increases the HDL by 2.94%. In Third visit, Atorvastatin 20mg increases the HDL by 6.56% while Atorvastatin 40mg increases the HDL by 2.85%. It shows that Atorvastatin 20mg is better than Atorvastatin 40mg.

Also it was found in second visit, Atorvastatin 20mg increases the HDL by 5.82% while Simvastatin 40mg increases the HDL by 11.93%. In Third visit, Atorvastatin 20mg increases the HDL by 6.56% while Simvastatin 40mg increases the HDL by 13.65%. It shows that Simvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that that in second visit Atorvastatin 40mg increases the HDL by 2.94% while Simvastatin 40mg increases the HDL by 11.93%. In Third visit, Atorvastatin 40mg increases the HDL by 2.85% while Simvastatin 40mg increases the HDL by 13.65%. It shows that Simvastatin 40mg is better than Atorvastatin 40 mg.

Changes in Low Density Lipoprotein levels

The present study was found that in second visit Atorvastatin 20mg reduces the LDL by 26.69% while Atorvastatin 40mg reduces the LDL by 41.93%.%. In Third visit, Atorvastatin 20mg reduces the LDL by 37.19% while Atorvastatin 40mg reduces the LDL by 58.18%. It shows that Atorvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 20mg reduces the low density lipoprotein by 26.69% while Simvastatin 40mg reduces the LDL by 61.19%. In Third visit, Atorvastatin 20mg reduces the LDL by 37.19% while Simvastatin 40mg reduces the LDL by 73.37%. It shows that Simvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 40mg reduces the LDL by 41.93% while Simvastatin 40mg reduces the LDL by 61.19%. In Third visit, Atorvastatin 40mg reduces the LDL by 58.18% while Simvastatin 40mg reduces the LDL by 73.37%. It shows that Simvastatin 40mg is better than Atorvastatin 40mg.

Changes in Triglycerides levels

The present study was found that in second visit Atorvastatin 20mg reduces the TG by 21.4% while Atorvastatin 40mg reduces the TG by 30.98%. In Third visit, Atorvastatin 20mg reduces the TG by 30.12% while Atorvastatin 40mg reduces the TG by 46.37%. It shows that Atorvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 20mg reduces the triglycerides by 21.4% while Simvastatin 40mg reduces the TG by 46.75%. In Third visit, Atorvastatin 20mg reduces the TG by 30.12% while Simvastatin 40mg reduces the TG by 55.94%. It shows that Simvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 40mg reduces the TG by 30.98% while Simvastatin 40mg reduces the TG by 46.75%. In Third visit, Atorvastatin 40mg reduces the TG by 46.37% while Simvastatin 40mg reduces the TG by 55.94%. It shows that Simvastatin 40mg is better than Atorvastatin 40mg.

Changes in Very Low Density Lipoprotein levels

The present study was found that in second visit, Atorvastatin 20mg reduces the VLDL by 21.76% while Atorvastatin 40mg reduces the VLDL by 30.72%. In Third visit, Atorvastatin 20mg reduces the VLDL by 30.57% while Atorvastatin 40mg reduces the VLDL by 46.37%. It shows that Atorvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit, Atorvastatin 20mg reduces the VLDL by 21.76% while Simvastatin 40mg reduces the VLDL by 46.62%. In Third visit, Atorvastatin 20mg reduces the VLDL by 30.57% while Simvastatin 40mg reduces the VLDL by 57.22%. It shows that Simvastatin 40mg is better than Atorvastatin 20mg.

Also it was found that in second visit Atorvastatin 40mg reduces the VLDL by 30.72% while Simvastatin 40mg reduces the VLDL by 46.62%. In Third visit, Atorvastatin 40mg reduces the VLDL by 46.37% while Simvastatin 40mg reduces the VLDL by 57.22%. It shows that Simvastatin 40mg is better than Atorvastatin 40mg.

Incidence of side effects

In this study, the side effects observed in the patients are:

- General Weakness
- Myalgia
- LFT Slightly Elevated
- Pedal Odema

In the present study, 70% of the patients who had taken Simvastatin 40mg showed General Weakness whereas in Atorvastatin 40mg study group, 43.5% of the patients showed General Weakness. In the Atorvastatin 20mg study group, only 10% of the patients showed General Weakness.

Also, 33.3% of the patients who had taken Simvastatin 40mg showed Myalgia, whereas in Atorvastatin 40mg study group, 26.7% of the patients showed Myalgia. In the Atorvastatin 20mg study group, only 3.3% of the patients showed Myalgia.

Also, 6.7% of the patients who had taken Simvastatin 40mg and Atorvastatin 40mg showed Slight Elevation in LFT.

Also, 6.7% of the patients who had taken Simvastatin 40mg showed Pedal Odema.

Thus the present study showed that the incidence of side effects was more in Simvastatin 40mg when compared to Atorvastatin 40mg and it was very less in Atorvastatin 20mg.

The results of the present study showed that Simvastatin 40mg produce sudden reductions in LDL-C, total cholesterol, Triglycerides, and an increase in HDL-C when compared to Atorvastatin 40mg but the incidence of side effects were more in Simvastatin 40mg.

Also it was showed that Atorvastatin 40mg produce sudden reductions in LDL-C, total cholesterol, Triglycerides when compared to Atorvastatin 20mg. But in increasing HDL-C, Atorvastatin 20mg is better when compared to Atorvastatin 40mg as shown in Table No: 50.

CONCLUSION

Patients treated with Simvastatin 40mg had significantly greater reductions in total cholesterol, low density lipoprotein, triglycerides, very low density lipoprotein and an increase in high density lipoprotein. But due to the high incidence of side effects, Simvastatin 40mg is not recommended for a longer period.

As the incidence of side effects of Atorvastatin 40mg is less when compared to Simvastatin 40mg, Atorvastatin 40mg is better than Simvastatin 40mg.

From this study, I found that for the patients who had underwent PTCA, the doctors usually advice to take Atorvastatin 40mg for the sudden reduction of lipid levels especially Low Density Lipoprotein and the Doctors advise to take Atorvastatin 40mg for approximately one year along with the Lifestyle modifications.

After the LDL-C reaches the desired margin (Approximately below 100mg/dl), the patients are advised to replace Atorvastatin 40mg with Atorvastatin 20mg. This is due to the fact that Atorvastatin 20mg increases HDL value than Atorvastatin 40mg.